TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	Attorney's Docket Number 02481.1669	
	U.S. Application No. 09/554267	
International Application. No. PCT/EP98/06868	International Filing Date October 29, 1998	Priority Date Claimed November 15, 1997

PCT

Title of Invention: ANTISENSE OLIGONUCLEOTIDES AGAINST TENASCIN FOR TREATING VITILIGO

Applicant(s) For DO/EO/US: Anuschirwan PEYMAN, Eugen UHLMANN, and Caroline WEISER

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.

16. [x] Other items or information:
    a. [ ] Verified Small Entity Statement.
    b. [ ] Copy of Notification of Missing Requirements.
    c. [x] Sequence Listing (21 sheets)

526 Rec'd PCT/PTO 12 MAY 2000

U.S. APPLICATION NO 09/554267	INTERNATIONAL APPLICATION NO.	ATTORNEY DOCKET NUMBER
	PCT/EP98/06868	02481.1669

17. [X] The following fees are submitted:	CALCULATIONS
Basic National Fee (37 CFR 1.492(a)(1)-(5)):	
Search Report has been prepared by the EPO or JPO.....$840.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$670.00	
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$690.00	
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$970.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).....$ 96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$840.00**
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

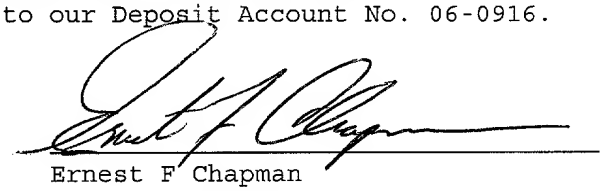
Claims	Number Filed	Number Extra	Rate	
Total Claims	57-20=	37	X $18.00	$666.00
Independent Claims	1 - 3=		X $78.00	$
Multiple dependent claim(s) (if applicable)			+$260.00	$260.00
		TOTAL OF ABOVE CALCULATIONS =		**$1766.00**
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)				$
		SUBTOTAL =		**$1766.00**
Processing fee of $130.00 for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).			+	$
		TOTAL NATIONAL FEE =		**$1766.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31).		$40.00 per property	+	$
		TOTAL FEES ENCLOSED =		**$1766.00**
		Amount to be refunded		$
		charged		$

a. [X] A check in the amount of **$ 1766.00** to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 06-0916. A duplicate copy of this sheet is enclosed.

The Commissioner is hereby authorized to charge any other fees due under 37 C.F.R. §1.16 or §1.17 during the pendency of this application to our Deposit Account No. 06-0916.



Ernest F Chapman
Reg. No. 25,961

Submitted: May 12, 2000

SEND ALL CORRESPONDENCE TO:
Finnegan, Henderson, Farabow
Garrett & Dunner, L.L.P.
1300 I Street, N.W.
Washington, D.C. 20005-3315
EFC/FPD/dvz

PATENT
Attorney Docket No. 02481.1669

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Nat'l Phase Application of PCT/EP 98/06868 filed Oct. 29, 1998	)	
Applicants: Anuschirwan PEYMAN et al.	)	
Serial No.: Not yet assigned	)	Group Art Unit: Not yet assigned
Filed: Herewith	)	Examiner: Not yet assigned
For: ANTISENSE OLIGONUCLEOTIDES AGAINST TENASCIN FOR TREATING VITILIGO	)	

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examining this application, please amend this application as follows:

IN THE CLAIMS:

Please cancel Claims 1-23 without prejudice or disclaimer. Please add Claims 24-44, as follows:

24. An oligonucleotide comprising 7 to 17 nucleotides, wherein the oligonucleotide binds to a nucleic acid which codes for one of the isoforms of human tenascin or parts thereof and inhibits its expression, and the physiologically tolerable salts of the oligonucleotide.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

25. The oligonucleotide according to claim 24, wherein the oligonucleotide binds to a region of the nucleic acid which comprises:

a) a part of the 5'-noncoding region optionally including a translation start,

b) a translation start optionally including a part of the coding region, or

c) a part of the coding region optionally including a part of the 3'-noncoding region.

26. The oligonucleotide according to claim 24, comprising a sequence selected from the group consisting of:

SEQ. ID NO. 2:	3'- GGTTTGGGTGGAGGTGG -5',
SEQ. ID NO. 3:	3'- GGAGGTGGTACCCCCGG -5',
SEQ. ID NO. 4:	3'- GGTGGTACCCCCGG -5',
SEQ. 10 NO. 5:	3'- GGAGGTGGTACCCC -5',
SEQ. 10 NO. 6:	3'-AGAAAGAACGAAAGGAA -5',
SEO. 10 NO. 7:	3'- GGAGGTGGTACC -5',
SEQ. ID NO. 8:	3'- GGAGCGATGGCTTCCA -5',
SEQ. ID NO. 9:	3'- AAAGGAACGGGAGCG -5',
SEQ. ID NO. 10:	3'- GGTCGGTTTGGGTGG -5',
SEQ. ID NO. 11:	3'- CTTACAGGTCCGTTGA -5,'
SEQ. ID NO. 12:	3'- GGCCGTGTTCGCTGT -5',
SEQ. ID NO. 13:	3'- TCACCCCTCTTTCTGG -5,'
SEQ. ID NO. 14:	3'- GGACACCGACACGG -5',
SEQ. ID NO. 15:	3'-AACGGGAGCGATGG-5',

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

SEQ. ID NO. 16. 3'- ATCTCGGGGTCGTC -5',

SEQ. ID NO. 17: 3'-AAAGAACGAAAGGAA-5',

SEQ. ID NO. 18: 3'- GGTGGTACCCC -5',

SEQ. ID NO. 19: 3'- CCCGGTACTGA -5', and

SEQ. ID NO. 20: 3'- CCACAGAAAGAAC -5'.

27. An oligonucleotide according to any one of claims 24, 25, or 26, wherein the oligonucleotide has one or more modifications.

28. The oligonucleotide according to claim 27, wherein the modifications are independently selected from the group consisting of:

a) the replacement of a phosphoric acid diester internucleoside bridge by a modified phospho bridge,

b) the replacement of a phosphoric acid diester internucleoside bridge by a "dephospho" bridge,

c) the replacement of a sugar phosphate unit by another unit,

d) the replacement of a β-D-2'-deoxyribose unit by a modified sugar unit,

e) the modification or the replacement of a natural nucleoside base by a modified nucleoside base,

f) the conjugation of the oligonucleotide to a molecule which adapts the properties of the oligonucleotide to a specific requirement,

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

g) the conjugation of the oligonucleotide to a 2'5'-bonded oligoadenylate or a derivative thereof, optionally conjugated via a linker, and

h) the introduction of a 3'-3' or 5'-5' inversion at the 3' or 5' end of the oligonucleotide.

29. The oligonucleotide according to claim 28, wherein the oligonucleotide contains one or more modification independently selected from the group consisting of:

a) the replacement of a phosphoric acid diester internucleoside bridge by a modified phospho bridge,

where a modified phospho bridge is a phosphorothioate, phosphorodithioate, $NR^1R^{1'}$-phosphoramidate, boranophosphate, phosphate-$(C_1$-$C_{21})$-O-alkyl ester, phosphate-$[(C_6$-$C_{12})$aryl-$(C_1$-$C_{21})$-O-alkyl] ester, $(C_1$-$C_8)$alkylphosphonate, or $(C_6$-$C_{12})$ arylphosphonate bridge,

where

R^1 and $R^{1'}$ are independently selected from the group comprising hydrogen, $(C_1$-$C_{18})$-alkyl, $(C_6$-$C_{20})$-aryl, $(C_6$-$C_{14})$-aryl-$(C_1$-$C_8)$-alkyl, or

R^1 and $R^{1'}$, together with the nitrogen atom carrying them, form a 5- to 6-membered heterocyclic ring which can additionally contain a further heteroatom from the group consisting of O, S, and N;

b) the replacement of a phosphoric acid diester internucleoside bridge by a "dephospho" bridge,

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

where a "dephospho" bridge is a formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethylhydrazo, dimethylenesulfone, or silyl bridge,

c) the complete or partial replacement of the sugar phosphate backbone (replacement of sugar phosphate units) by other units,

where another unit is suitable for synthesizing a "morpholine derivative" oligomer, a polyamide nucleic acid ("PNA"), or a phosphomonoacid ester nucleic acid,

d) the replacement of a β-D-2'-deoxyribose unit by a modified sugar unit,

where a modified sugar unit is an α-D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-O-(C_1-C_6)alkylribose, 2'-O-(C_2-C_6)alkenylribose, 2'-[O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl]ribose, 2'-NH_2- 2'-deoxyribose, β-D-xylofuranose, α-arabinofuranose, 2,4-dideoxy-β-D-erythro-hexopyranose, a carbocyclic sugar analog, an open-chain sugar analog, or a bicyclo sugar analog,

e) the replacement of a natural nucleoside base by a modified nucleoside base,

where a modified nucleoside base is 5-(hydroxymethyl)uracil, 5 aminouracil, pseudouracil, dihydrouracil, 5-(C_1-C_6-alkyluracil, 5-(C_2-C_6)-alkenyluracil, 5-(C_2-C_6)-alkynyluracil, 5-(C_1-C_6)-alkylcytosine, 5-(C_2-C_6)-alkenylcytosine, 5-(C_2-C_6)-alkynylcytosine, 5-fluorouracil, 5-fluorocytosine, 5-chlorouracil,

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

5-chlorocytosine, 5-bromouracil, 5-bromocytosine, a 7-deaza-7-substituted purine, or a 7-deaza-8-substituted purine,

f) conjugation to a molecule,

where the molecule is a polylysine, intercalator, fluorescent molecule, crosslinker, lipophilic molecule, lipid, steroid, vitamin, polyethylene glycol, oligoethylene glycol, (C_{12}-C_{18})-alkyl phosphate diester, or -O-CH_2-CH(OH)-O-(C_{12}-C_{18})-alkyl group,

g) conjugation to a 2'5'-linked oligoadenylate or a derivative thereof

where a 2'5'-linked oligoadenylate or a derivative thereof is a 2'5'-linked triadenylate, 2'5'-linked tetraadenylate, 2'5'-linked pentaadenylate, or cordycepin (2'5'-linked 3'-deoxyadenylate), where the conjugation optionally takes place via a linker and where the 5'-end of the 2'5'-linked oligoadenylate optionally contains a phosphate, diphosphate, or triphosphate group, and

h) the introduction of a 3'-3' or 5'-5' inversion at the 3'- or 5'- end of the oligonucleotide.

30. The oligonucleotide according to claim 28, wherein 1 - 5 terminal internucleoside bridges are modified at the 5- or 3'- end of the oligonucleotide.

31. The oligonucleotide according to claim 28, wherein the internucleoside bridges located at the 3'- or 5'- end of nonterminal nucleosides which contain a pyrimidine base are modified.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

32. The oligonucleotide according to claim 28,comprising a sequence selected from the group consisting of:

SEQ ID NO. 21:	3'- GsGsTsTsTGGGTsGGAGGsTsGsG -5',
SEQ ID NO. 22.	3'- GsGsAsGGTsGGTsACsCCsCCsGsG -5',
SEQ ID NO. 23	3'- GsGsTGGTsACsCsCCsCsGsG -5',
SEQ ID NO. 24:	3'- GsGsAGGTsGGTsACsCsCsC -5,
SEQ ID NO. 25:	3'- AsGsAAAGAAsCsGAAAGGsAsA -5',
SEQ ID NO. 26:	3'- GsGsAGGTsGGTsAsCsC -5',
SEQ ID NO. 27:	3'- GsGsAGCsGATsGGCsTsTsCsCsA -5',
SEQ ID NO. 28:	3'- AsAsAGGAACsGGGAGsCsG -5',
SEQ ID NO. 29:	3'- GsGsTCGGTsTsTGGGTsGsG -5',
SEQ ID NO. 30:	3'- CsTsTACAGGTsCsCGTsTsGsA -5',
SEQ ID NO. 31:	3'- GsGsCsCGsTGTsTCGCsTsGsT -5',
SEQ ID NO. 32:	3'- TsCsACsCCsCTsCsTTsTsCsTsGsG -5',
SEQ ID NO. 33:	3'- GsGsAsCACsCGACsACsGsG -5',
SEQ ID NO. 34:	3'- AsAsCsGGGAGCGATsGsG -5',
SEQ ID NO. 35:	3'- AsTsCsTCGGGGTsCsGsTsC -5',
SEQ ID NO. 36:	3'- AsAsAGAACsGAAAGGsAsA -5',
SEQ ID NO. 37:	3'- GsGsTGGTsACsCsCsC -5',
SEQ ID NO. 38:	3'- CsCsCsGGTsACsTsGsA -5, and
SEQ ID NO. 39:	3'- CsCsAsCAGAAAGsAsAsC -5',

where "s" indicates the position of a modified internucleoside bridge.

33. The oligonucleotide according to claim 28, comprising a sequence selected from the group consisting of:

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

SEQ ID NO. 40: 3'- GyGyTyTyTyGxGxGxTxGxGxAxGyGyTyGyG -5',

SEQ ID NO. 41: 3'- GyGyAyGyGyTxGxGxTxAxCxCxCyCyCyGyG -5',

SEQ ID NO. 42: 3'- GyGyTxGxGxTxAxCxCxCxCyCyGyG -5',

SEQ ID NO. 43: 3'- GyGyAyGyGxTxGxGxTxAxCyCyCyC -5',

SEQ ID NO. 44: 3'- AyGyAyAxAxGxAxAxCxGxAxAxAyGyGyAyA -5',

SEQ ID NO. 45: 3'- GyGyAxGxGxTxGxGxTxAyCyC -5',

SEQ ID NO. 46: 3'- GyGyAxGxCxGxAxTxGyGyCyTyTyCyCyA -5',

SEQ ID NO. 47: 3'- AyAyAyGxGxAxAxCxGxGyGyAyGyCyG -5',

SEQ ID NO. 48: 3'- GyGyTyCxGxGxTxTxTxGxGyGyTyGyG -5',

SEQ ID NO. 49: 3'- CyTyTyAxCxAxGxGxTxCxCxGyTyTyGyA -5',

SEQ ID NO. 50: 3'- GyGyCyCxGxTxGxTxTxCxGyCyTyGyT -5',

SEQ ID NO. 51: 3'- TyCyAyCxCxCxCxTxCxTxTyTyCyTyGyG -5',

SEQ ID NO. 52: 3'- GyGyAyCxAxCxCxGxAxCxAyCyGyG -5',

SEQ ID NO. 53: 3'- AyAyCyGxGxGxAxGxCxGxAyTyGyG -5',

SEQ ID NO. 54: 3'- AyTyCyTxCxGxGxGxGxTxCxGyTyC -5',

SEQ ID NO. 55: 3'- AyAyAyGxAxAxCxGxAxAxAxGyGyAyA -5',

SEQ ID NO. 56: 3'- GyGyTxGxGxTxAxCxCyCyC -5',

SEQ ID NO. 57: 3'- CyCxCxGxGxTxAxCyTyGyA -5', and

SEQ ID NO. 58: 3'-CyCyAxCxAxGxAxAxAxGyAyAyC-5',

where

"x" independently of one another represents a phosphodiester internucleoside bridge or a modified internucleoside bridge and

"y" independently of one another represents the replacement of a sugar phosphate unit or of a β-D-2'-deoxyribose unit, the modified β-D-2'-deoxyribose unit being located at the 3'- end of "y".

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

34. The oligonucleotide according to claim 33, where "y" represents 2' O-methyl-, 2'-O-propyl- or 2'-methoxyethoxyribose, or a PNA unit.

35. The method for inhibiting the expression of tenascin by administering an oligonucleotide according to any one of claim 24-26.

36. The method for therapeutically treating vitiligo by administering an oligonucleotide according to any one of claims 24-26.

37. The method for therapeutically treating hypopigmentation disorders, psoriasis, cancer, inflamatory disorders, or cardiovascular disorders by administering an oligonucleotide according to any one of claims 24-26.

38. A pharmaceutical comprising an oligonucleotide according to any one of claims 24-26 and, if appropriate, one or more pharmaceutical vehicles, optionally including additives.

39. The method for inhibiting the expression of tenascin by administering an oligonucleotide according to any one of claims 24-26, in combination with photochemotherapy, the transplantation of cultured melanocytes, treatment with steroids, or treatment with placenta extracts.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

40. The method for therapeutically treating vitiligo by administering an oligonucleotide according to any one of claims 24-26, in combination with photochemotherapy, the transplantation of cultured melanocytes, treatment with steroids, or treatment with placenta extracts.

41. A process for the production of a pharmaceutical, wherein an efficacious dose of one or more oligonucleotides according to any one of claims 24-26 is mixed with one or more pharmaceutical vehicles and/or additives.

42. A process for the preparation of an oligonucleotide according to any one of claims 24-26, the oligonucleotide being chemically synthesized on a solid phase.

43. A diagnostic comprising one or more oligonucleotides according to any one of claims 24-26.

44. A test kit comprising one or more oligonucleotides according any one of claims 24-26.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

REMARKS

I. Status of the Claims

Original claims 1-23 have been canceled without prejudice or disclaimer. New claims 24-42 have been added to more particularly point out and distinctly claim what Applicants regard as their invention and cure improper multiple dependency of claims. No new matter has been added. The new claims are supported in the original claims and in the application as follows:

Claim No.	Support
24	Claim 1 and Page 3, lines 8-11
25	Claim 2
26	Claim 3
27	Claim 4
28	Claim 5 and Page 8, lines 37-38
29	Claim 6
30	Claim 8
31	Claim 9
32	Claim 10
33	Claim 11
34	Claim 12
35	Claim 13 and Page 3, lines 25-29
36	Page 16, lines 12-13
37	Page 16, lines 13-19
38	Claim 18
39	Claim 19
40	Page 16, lines 28-34
41	Claim 20
42	Claim 21
43	Claim 22
44	Claim 23

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

II. Conclusion

Applicants await action on the merits. If there are any additional fees due in connection with the filing of this Preliminary Amendment, please charge those fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: _____
Carol P. Einaudi
Reg. No. 32,220

Dated: May 12, 2000

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
202-408-4000

Antisense oligonucleotides against tenascin for the treatment of vitiligo

The invention relates to specific, optionally modified oligonucleotides having a length of up to 18 nucleotides, preferably a length of 7-15 nucleotides, which correspond to sections of tenascin-coding sequences and can bind to these sequences, to their preparation and to the use thereof, for example for the specific inhibition of the expression of tenascin and for the production of medicaments which can be used for the treatment of vitiligo.

Vitiligo is understood as meaning an acquired lack of melanocytes, by means of which hypopigmented areas of skin result, which as a rule are sharply demarcated and often symmetrically arranged, form one or two spots or cover almost the entire skin. The hair in hypopigmented regions is normally white and appears white even in the Wood light. The affected skin sites are susceptible to sunburn. The cause of the disorder is unknown. Although vitiligo is considered as a disease which is acquired in the course of life, a familial cluster is occasionally found (autosomally dominant, with incomplete penetrance and variable pronouncement). It can also follow an unusual physical trauma, in particular a skull injury. The association of vitiligo with Addison's disease, diabetes mellitus, pernicious anemia or thyroid gland dysfunction and the increased occurrence of antibodies against thyroglobulin, cells of the adrenal gland and border cells of the stomach in the serum have led to an immunological or neurochemical cause being suspected. Antibodies against melanin were found in some patients.

All available therapeutic methods lead to satisfactory therapeutic results in only some of the patients (F. Wach et al., H+G 71 (1996) 206). The present therapies (S.P.W. Kumarasinghe, Ceylon Medical Journal 40 (1995) 94) include photochemotherapies (PUVA) for example with methoxypsoralen, phenylalanin or khellin, the transplantation of cultured melanocytes, epidermal grafting, and treatment with steroids or placenta extracts. Recently, treatment with pseudocatalase was reported (Schallreuter et al., Dermatology 190 (1995) 223). Small foci can also be covered with cosmetic make-up or tannic acid solutions.

Poole et al. (British Journal of Dermatol. 137 (1997) 171) were able to show

that the vitiligo-affected skin has a high content of tenascin in comparison with normal skin. The high tenascin content can contribute to the loss of pigmentation and prevent repigmentation. Tenascin (Crossin, J. Cell. Biol. 61 (1996) 592) is an extracellular matrix glycoprotein, which consists of six identical subunits which are linked to the amino terminus via disulfide bridges. The tenascin subunits have a characteristic domain structure: a cysteine-rich sequence at the amino-terminal end is followed by three sequence sections, in each case constructed of repeating units, made of units homologous to EGF, of units homologous to fibronectin (type III) and of units homologous to fibrinogen.

A number of isoforms of the tenascin subunits exists (designated below as tenascin isoforms), which differ in the number of repeating units which are homologous to fibronectin type III. These isoforms are formed by alternative splicing of the tenascin pre-mRNA and subsequent translation of the various splice variants (A. Leprini et al., Perspectives in Developmental Neurobiology 2 (1994) 117-123). A cDNA from human tenascin was described (sequence in Table 1) by A. Siri et al. (Nucl. Acids Res. 19 (1991) 525-531). This cDNA is stored under the accession number X56160 in gene databases and can be obtained under this number, for example under EMBL/Genbank/DDBJ/NBRF-PIR. This cDNA contains a sequence section which codes for 12 repeating units which are homologous to fibrinogen type III. The cDNAs of the other isoforms of human tenascin are truncated in this sequence section and code for less than 12 of these repeating units.

The expression of tenascin is limited spatially and temporally and a significance is ascribed to it during the development of an organism and in pathological changes (Crossin, vide supra). Such pathological changes are, for example, vitiligo, tumors and inflammation.

Antisense oligonucleotides offer one possibility for the regulation of gene expression (E. Uhlmann and A. Peyman, Chemical Reviews 90, 543 (1990); S. Agrawal. TIBTECH 1996, 376). WO 94/21664 (L. Denner et al.) describes antisense oligonucleotides against tenascin, which are employed for the inhibition of the proliferation of the smooth cell musculature. The oligonucleotides described there have a length of at least 18 nucleotides.

It was an object of the present invention to make available novel oligonucleotides which have advantageous properties and which can be used for the complete and/or partial inhibition of the gene expression of tenascin.

It has surprisingly been found that oligonucleotides which have a length of up to 18 nucleotides can effectively influence the expression of tenascin. The present invention relates to oligonucleotides having 7-17 nucleotide units which are optionally modified. In particular embodiments of the invention, the oligonucleotide has a length of 17, 16, 15, 14, 13, 12, 11, 10, 9, 8 or 7 nucleotides. The oligonucleotide corresponds to sections of tenascin-coding sequences (i.e. the oligonucleotide has a sequence which is complementary to the corresponding section of a tenascin-coding sequence) and the oligonucleotide binds specifically to this tenascin-coding sequence (nucleic acid), for example to the tenascin gene and/or tenascin mRNA and/or tenascin cDNA, the tenascin-coding sequence preferably being of human origin (e.g. human tenascin gene, human tenascin mRNA, human tenascin cDNA). The section of the tenascin-coding sequence which corresponds to the oligonucleotide or is complementary to the oligonucleotide preferably has a length of 17, 16, 15, 14, 13, 12, 11, 10, 9, 8 or 7 nucleotide units (this applies in particular to the determination of the length of a modified and/or chimeric oligonucleotide or of oligonucleotide analogs).

A particular embodiment of the invention relates to an oligonucleotide which binds to a nucleic acid which codes for one of the isoforms of human tenascin or parts thereof and inhibits its expression, where the oligonucleotide has a length of 7 to 15 nucleotides and can optionally be modified, and the physiologically tolerable salts of the oligonucleotide.

A particular embodiment of the invention relates to an oligonucleotide which is directed against one or more specific regions of a tenascin-coding sequence, for example the translation start, the 5'-nontranslated region, the coding region and/or the 3'-noncoding region. In a particular embodiment of the invention, the oligonucleotide can also be directed against one or more regions of a tenascin-coding sequence which codes, for example, for certain domains of the tenascin, for example against the cysteine-rich domain, against a domain homologous to EGF, against a domain

homologous to fibronectin type III and/or against a domain homologous to fibrinogen.

One embodiment of the invention relates to an oligonucleotide which binds to a nucleic acid which codes for one of the isoforms of human tenascin or parts thereof and inhibits its expression, where the oligonucleotide can bind to a region of the nucleic acid which comprises

a) a part of the 5'-noncoding region and/or the translation start or

b) the translation start and/or a part of the coding region or

c) a part of the coding region and/or a part of the 3'-noncoding region.

The invention relates in particular to an oligonucleotide which corresponds to a sequence section of the human cDNA according to SEQ ID NO. 1 (Table 1). The invention furthermore relates to an oligonucleotide which corresponds to a sequence section of the cDNA which is stored in gene databases under the accession number X56160.

In specific embodiments of the invention, an oligonucleotide can have, for example, one of the following sequences or parts thereof:

SEQ ID NO. 2: 3'- GGTTTGGGTGGAGGTGG -5'

SEQ ID NO. 3: 3'- GGAGGTGGTACCCCCGG -5'

SEQ ID NO. 4: 3'- GGTGGTACCCCCGG -5'

SEQ ID NO. 5: 3'- GGAGGTGGTACCCC -5'

SEQ ID NO. 6: 3'- AGAAAGAACGAAAGGAA -5'

SEQ ID NO. 7: 3'- GGAGGTGGTACC -5'

SEQ ID NO. 8: 3'- GGAGCGATGGCTTCCA -5'

SEQ ID NO.. 9: 3'- AAAGGAACGGGAGCG -5'

SEQ ID NO. 10: 3'- GGTCGGTTTGGGTGG -5'

SEQ ID NO. 11: 3'- CTTACAGGTCCGTTGA -5'

SEQ ID NO. 12: 3'- GGCCGTGTTCGCTGT -5'

SEQ ID NO. 13: 3'- TCACCCCTCTTTCTGG -5'

SEQ ID NO. 14: 3'- GGACACCGACACGG -5'

SEQ ID NO. 15: 3'- AACGGGAGCGATGG -5'

SEQ ID NO. 16: 3'- ATCTCGGGGTCGTC -5'

SEQ ID NO. 17: 3'- AAAGAACGAAAGGAA -5'

SEQ ID NO. 18: 3'- GGTGGTACCCC -5'

SEQ ID NO. 19: 3'- CCCGGTACTGA -5' and

SEQ ID NO. 20: 3'- CCACAGAAAGAAC -5'.

The sequences SEQ ID NO. 2 to SEQ ID NO. 20 correspond to sections of the tenascin-coding cDNA, as is shown in Table 1. An oligonucleotide which has one of the sequences SEQ ID NO. 2 to SEQ ID NO. 20 is complementary to a corresponding section of a tenascin-coding nucleic acid, e.g. a human tenascin cDNA, and can bind to this nucleic acid. Sequences SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 7 and SEQ ID NO. 18 are examples of oligonucleotides which have a sequence which is directed against the translation start of the tenascin-coding sequences.

The invention also relates to derivatives of an oligonucleotide, for example its salts, in particular its physiologically tolerable salts. Physiologically tolerable salts are understood as meaning compounds which are readily soluble, soluble or poorly soluble in water, for example according to the definition in the "Deutsches Arzneibuch" [German Pharmacopeia] (9th

Edition 1986, official edition, Deutscher Apotheker Verlag Stuttgart), page 19. A specific embodiment of the invention relates to the sodium salt of the oligonucleotide according to the invention. Derivatives are also modified oligonucleotides.

An oligonucleotide can be synthesized completely or partially from the natural nucleotides adenosine phosphate, guanosine phosphate, inosine phosphate, cytidine phosphate, uridine phosphate and thymidine phosphate. One embodiment of the invention relates to an oligonucleotide which is synthesized from the natural nucleotides adenosine, guanosine, inosine, cytidine, uridine and thymidine and in which the nucleosides are linked to one another via phosphoric acid diester internucleoside bridges ("phosphoric acid diester bridges").

In other embodiments of the invention, an oligonucleotide can optionally contain one or more modifications, for example chemical modifications. An oligonucleotide can have a number of identical and/or different modifications. Modifications can be localized on certain nucleotide positions (nucleobase and/or β-D-2'-deoxyribose unit) and/or certain internucleoside bridges.

Examples of chemical modifications are known to the person skilled in the art and are described, for example, in E. Uhlmann and A. Peyman, Chemical Reviews 90 (1990) 543 and "Protocols for Oligonucleotides and Analogs" Synthesis and Properties & Synthesis and Analytical Techniques, S. Agrawal, Ed, Humana Press, Totowa, USA 1993, S.T. Crooke, F. Bennet, Ann. Rev. Pharmacol. Toxicol. 36 (1996) 107-129 and J. Hunziber and C. Leumann (1995) Mod. Synt. Methods, 7, 331-417.

The chemical modification of an oligonucleotide can mean, for example,
a) the complete or partial replacement of the phosphoric acid diester bridges (internucleoside bridges) by modified phospho bridges, phosphorothioate, phosphorodithioate, $NR^1R^{1'}$-phosphoramidate, boranophosphate, phosphate-(C_1-C_{21})-O-alkyl ester, phosphate-[(C_6-C_{12})-aryl-(C_1-C_{21})-O-alkyl] ester, (C_1-C_8)alkylphosphonate and/or (C_6-C_{12})-arylphosphonate bridges being examples of modified phospho bridges, where
R^1 and $R^{1'}$ independently of one another are hydrogen, (C_1-C_{18})-alkyl, (C_6-C_{20})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl, preferably hydrogen, (C_1-C_8)-

alkyl and/or methoxyethyl, particularly preferably hydrogen, (C_1-C_4)-alkyl and/or methoxyethyl

or

R^1 and $R^{1'}$, together with the nitrogen atom carrying them, form a 5- to 6-membered heterocyclic ring, which can additionally contain a further heteroatom from the group consisting of O, S and N;

and/or

b) the complete or partial replacement of the 3' and/or 5' phosphoric acid diester internucleoside bridges ("phosphoric acid diester bridges") by "dephospho" bridges (described, for example, in Uhlmann, E. and Peyman, A. in "Methods in Molecular Biology", Vol. 20, "Protocols for Oligonukleotides and Analogs", S. Agrawal, Ed., Humana Press, Totowa 1993, Chapter 16, 355ff), formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethylhydrazo, dimethylenesulfone and/or silyl groups being examples of dephospho bridges;

and/or

c) the complete or partial replacement of the sugar phosphate backbone (replacement of sugar phosphate units) by other units, the other unit being suitable, for example, to synthesize a "morpholine derivative" oligomer (described, for example, in E.P. Stirchak et al., Nucleic Acids Res. 17 (1989) 6129) (i.e. replacement by a morpholino derivative unit) and/or being suitable to synthesize a polyamide nucleic acid ("PNA") described, for example, in P.E. Nielsen et al., Bioconj. Chem. 5 (1994) 3 (EP 0 672 677) (i.e. replacement by a PNA unit, for example 2-aminoethylglycine) and/or being suitable to synthesize a phosphomonoacid ester nucleic acid ("PHONA", "PMENA") (described, for example, in Peyman et al., Angew. Chem. Int. Ed. Engl. 35 (1996) 2632-2638, EP 0 739 898) (i.e. replacement by a PHONA unit);

and/or

d) the complete or partial replacement of the β-D-2'-deoxyribose (β-D-2'-deoxyribose unit) by modified sugar units, α-D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-O-(C_1-C_6)alkylribose, preferably 2'-O-methylribose, 2'-O-(C_2-C_6alkenylribose, 2'-[O-(C_1-C_6) alkyl-O-(C_1-C_6alkyl)-ribose, 2'-NH_2-2'-deoxyribose, β-D-xylofuranose, α-arabinofuranose, 2,4-dideoxy-β-D-erythrohexopyranose, carbocyclic sugar analogs (described, for example, in Froehler, J.Am.Chem.Soc. 114 (1992) 8320), open-chain sugar analogs (described, for example, in Vandendriessche et al., Tetrahedron 49 (1993) 7223) and bicyclo sugar analogs (described, for

analogs (described, for example, in M. Tarkov et al., Helv. Chim. Acta 76 (1993) 481) being examples of modified sugar units;

and/or

e) the modification or the complete or partial replacement of the natural nucleoside bases by modified (nucleoside) bases ("nucleobases"), 5-(hydroxymethyl)uracil, 5-aminouracil, pseudouracil, dihydrouracil, 5-(C_1-C_6-alkyluracil, 5-(C_2-C_6)-alkenyluracil, 5-(C_2-C_6)alkynyluracil, 5-(C_1-C_6)alkylcytosine, 5-(C_2-C_6)alkenylcytosine, 5-(C2-C6)alkynylcytosine, 5-fluorouracil, 5-fluorocytosine, 5-chlorouracil, 5-chlorocytosine, 5-bromouracil, 5-bromocytosine, 7-deaza-7-substituted purines, 7-deaza-8-substituted purines, 8-azapurines, 2,4-diaminopurines, 5-bromocytosine, 5-bromouracil, 5-chlorocytosine, 5-chlorouracil, 5-fluorocytosine, 5-fluorouracil, hypoxanthine and uracil being examples of modified bases;

and/or

f) the conjugation to one or more molecules (oligonucleotide conjugates) which adapt the property(ies) of the oligonucleotide to specific requirements or favorably influence the properties (e.g. cell penetration, nuclease stability, affinity for the tenascin-coding target sequence, pharmacokinetics) of the oligonucleotide (e.g. antisense oligonucleotide, triple helix-forming oligonucleotide) and/or in the hybridization of the oligonucleotide on the target sequence can attack this with binding and/or crosslinking, polylysine, intercalators such as pyrene, acridine, phenazine, phenanthridine, fluorescent compounds such as fluorescein, crosslinkers such as psoralen, azidoproflavine, lipophilic molecules such as (C_{12}-C_{20})alkyl, lipids such as 1,2-dihexadecyl-rac-glycerol, steroids such as cholesterol, testosterone, vitamins such as vitamin E, poly- or oligoethylene glycol, (C_{12}-C_{18})alkyl phosphate diesters and -O-CH_2-CH(OH)-O-(C_{12}-C_{18})-alkyl being examples of molecules which can be conjugated to an oligonucleotide, where such molecules can be conjugated to the oligonucleotide at the 5' and/or at the 3' end and/or within the sequence, e.g. via a nucleobase;

and/or

g) the conjugation to a 2'5'-linked oligoadenylate or a derivative thereof, a 2'5'-linked triadenylate, a 2'5'-linked tetraadenylate, a 2'5'-linked pentaadenylate etc. being examples of 2'5'-linked oligoadenylates and cordycepin (2'5'-linked 3'-deoxyadenylate) being an example of a derivative of a 2'5'-linked oligoadenylate, the conjugation preferably taking place via a linker, where the 5'-end of the 2'5'-linked oligoadenylate can preferably be a phosphate, diphosphate or triphosphate group, where the linker, for

example, can be an oligoethylene glycol, triethylene glycol, tetraethylene glycol and hexaethylene glycol being examples of oligoethylene glycol linkers;

and/or

h) the introduction of a 3'-3' and/or 5'-5' inversion at the 3' and/or at the 5' end of the oligonucleotide, this type of chemical modification being known to the person skilled in the art and being described, for example, in M. Koga et al., J. Org. Chem. 56 (1991) 3757.

In preferred embodiments of the invention, the oligonucleotide has one or more chemical modifications which independently of one another are selected from

a) the complete or partial replacement of the phosphoric acid diester bridges by phosphorothioate and/or (C_1-C_8)alkylphosphonate bridges,

b) the complete or partial replacement of the sugar phosphate backbone by PNA units and/or PHONA units,

c) the complete or partial replacement of the β-D-2'-deoxyribose units by 2'-F-2'-deoxyribose, 2'-O-(C_1-C_6)alkylribose and/or 2'-[O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl]ribose,

d) the complete or partial replacement of the natural nucleoside bases by 5-(C_2-C_6)-alkynyluracil and/or 5-(C_2-C_6)alkynylcytosine,

e) the conjugation of the oligonucleotide to one or more molecules which independently of one another can be selected from the group comprising lipophilic molecules, e.g. (C_{12}-C_{20})alkyl, lipids, e.g. 1,2-dihexadecyl-rac-glycerol, steroids, e.g. cholesterol and/or testosterone, vitamins, e.g. vitamin E, poly- or oligoethylene glycol, (C_{12}-C_{18})-alkyl phosphate diesters and-O-CH_2-CH(OH)-O-(C_{12}-C_{18})-alkyl and

f) one or more 3'-3' inversions at the 3' end of the oligonucleotide,

In another preferred embodiment of the invention, the oligonucleotide has one or more chemical modifications which independently of one another can be selected from the group comprising

a) the complete or partial replacement of the phosphoric acid diester bridges (phosphodiester bridges) by phosphorothioate bridges,

b) the complete or partial replacement of the β-D-2'-deoxyribose units by 2'-F-2'-deoxyribose, 2'-O-(C_1-C_6)alkylribose and/or 2'-[O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl]ribose,

c) conjugation to lipophilic molecules, e.g. (C_{12}-C_{20})-alkyl, to lipids, e.g. 1,2-dihexadecyl-rac-glycerol, to (C_{12}-C_{18})alkyl phosphate diesters and/ or to -O-CH_2-CH(OH)-O-(C_{12}-C_{18})-alkyl.

Processes for the preparation of an oligonucleotide conjugate are known to the person skilled in the art and are described, for example, in Uhlmann, E. & Peyman, A., Chem. Rev. 90 (1990) 543 and/or M. Manoharan in "Antisense Research and Applications", Crooke and Lebleu, Eds., CRC Press, Boca Raton, 1993, Chapter 17, p.303ff. and/or EP-A 0 552 766.

In a particular embodiment of the invention, an oligonucleotide is made available which can have one or more modifications and which has one of the sequences SEQ ID NO. 2 - SEQ ID NO. 20 or which corresponds to one of the sequences SEQ ID NO. 2 to SEQ ID NO. 20 or which corresponds to the appropriate sequence sections of a tenascin-coding sequence and can bind to this section of the tenascin-coding sequence.

In a particular embodiment of the invention, oligonucleotide is made available in whose sequence each nucleotide (base and/or sugar and/or internucleoside bridge) is modified. In a particular embodiment of the invention, for example, the oligonucleotide is completely synthesized from phosphorothioates (universally modified phosphorothioate, all internucleoside bridges modified). In a further specific embodiment of the invention, an oligonucleotide is made available which corresponds to one of the sequences SEQ ID NO. 2 - SEQ ID NO. 20, but where the phosphodiester bridges between the individual nucleosides (i.e. the internucleoside bridges between the individual nucleosides) are completely replaced by phosphorothioate bridges (i.e. phosphorothioate groups between the nucleosides).

In a further particular embodiment of the invention, an oligonucleotide is made available by only replacing some of the phosphodiester bridges by phosphorothioate bridges. In particular, the invention comprises oligonucleotides which are only minimally (or partially) modified. The principle of the minimally modified oligonucleotides is described in A. Peyman, E. Uhlmann, Biol. Chem. Hoppe-Seyler, 377 (1996) 67-70. In this case, 1-5, preferably 1-3 terminal nucleotide units (preferably the corresponding internucleoside bridges) at the 5' and/or at the 3' end and, if appropriate, additionally selected internal pyrimidine positions or preferably the corresponding internucleoside bridges which are located at the 3' and/or 5' end of the corresponding pyrimidine nucleoside, are modified or replaced, internucleoside bridges preferably being replaced by

phosphorothioate bridges. Oligonucleotides minimally modified in this way have particularly advantageous properties, for example they exhibit particular nuclease stability on minimal modification.

A particular embodiment of the invention relates to an oligonucleotide in which selected internucleoside bridges are replaced by modified internucleoside bridges, preferably by phosphorothioate bridges.

The invention relates to an oligonucleotide in which either

a) only certain phosphodiester internucleoside bridges or
b) all phosphodiester internucleoside bridges

are modified.

The invention furthermore relates to an oligonucleotide in which 1 – 5 terminal internucleoside bridges are modified at the 5' and/or at the 3' end of the oligonucleotide. The invention also relates to an oligonucleotide in which the internucleoside bridges located at the 3' and/or 5' end of nonterminal nucleosides which contain a pyrimidine base (internal pyrimidine nucleosides) are modified.

Specific embodiments of the invention comprise a minimally modified oligonucleotide which has one of the sequences selected from the group consisting of the sequences SEQ ID NO. 21 to SEQ ID NO. 39, where

SEQ ID NO. 21: is 3'- GsGsTsTsTGGGTsGGAGGsTsGsG -5',

SEQ ID NO. 22: is 3'- GsGsAsGGTsGGTsACsCCsCCsGsG -5',

SEQ ID NO. 23: is 3'- GsGsTGGTsACsCsCCsCsGsG -5',

SEQ ID NO. 24: is 3'- GsGsAGGTsGGTsACsCsCsC -5',

SEQ ID NO. 25: is 3'- AsGsAAAGAAsCsGAAAGGsAsA -5',

SEQ ID NO. 26: is 3'- GsGsAGGTsGGTsAsCsC -5',

SEQ ID NO. 27: is 3'- GsGsAGCsGATsGGCsTsTsCsCsA -5',

SEQ ID NO. 28: is 3'- AsAsAGGAACsGGGAGsCsG -5',

SEQ ID NO. 29: is 3'- GsGsTCGGTsTsTGGGTsGsG -5',

SEQ ID NO. 30: is 3'- CsTsTACAGGTsCsCGTsTsGsA –5',

SEQ ID NO. 31: is 3'- GsGsCsCGsTGTsTCGCsTsGsT -5',

SEQ ID NO. 32: is 3'- TsCsACsCCsCTsCsTTsTsCsTsGsG -5',

SEQ ID NO. 33: is 3'- GsGsAsCACsCGACsACsGsG -5',

SEQ ID NO. 34: is 3'- AsAsCsGGGAGCGATsGsG -5',

SEQ ID NO. 35: is 3'- AsTsCsTCGGGGTsCsGsTsC –5',

SEQ ID NO. 36: is 3'- AsAsAGAACsGAAAGGsAsA -5',

SEQ ID NO. 37: is 3'- GsGsTGGTsACsCsCsC -5',

SEQ ID NO. 38: is 3'- CsCsCsGGTsACsTsGsA -5',

SEQ ID NO. 39: is 3'- CsCsAsCAGAAAGsAsAsC-5' and

"s" indicating the position of a modified internucleoside bridge or dephospho bridge, "s" preferably indicating the position of a phosphorothioate bridge.

The sequences SEQ ID NO. 21 to SEQ ID NO. 39 correspond to the sequences SEQ ID NO. 2 - SEQ ID NO. 20, i.e. they can bind to the same regions of a tenascin-coding sequence, where, however, in contrast to the SEQ ID NO. 2-20, some of the phosphodiester bridges are replaced by modified phosphodiester bridges or dephospho bridges, preferably by phosphorothioate bridges (in the sequence marked by an "s").

A further embodiment of the invention relates to chimeric oligonucleotides. A chimeric oligonucleotide is synthesized from at least two different sequence sections, for example from a DNA section and a modified section, e.g. a PNA section and/or a PHONA section. These different sections impart particular properties to the entire oligonucleotide.

A particular form of chimeric oligonucleotides is described, for example, in Matteucci and Wagner, Nature 384 SUPP (1996) 20-22. A chimeric oligonucleotide can contain, for example,

1. a so-called core sequence, which consists of approximately seven nucleotides and which can activate the RNase H, and
2. one or more flanking sequences which increase the affinity, specificity and/or nuclease stability of the oligonucleotide.

For example, the core sequence can have internucleoside bridges modified in certain positions, for example the core sequence can contain phosphorothioate and/or phosphodiester bridges. Suitable flanking sequences are, for example, sequences in which the sugar phosphate backbone (replacement of one or more sugar phosphate units) and/or β-D-2'-deoxyribose units are replaced. Suitable flanking sequences are, for example, PNAs and/or 2'-O-alkyl derivatives such as, for example, 2'-O-methyl and/or 2'-O-propyl and/or 2'-methoxyethoxy derivatives.

A particular embodiment of the invention relates to a chimeric oligonucleotide which has one of the sequences SEQ ID NO. 40 - SEQ ID NO. 58, where

x independently of one another represents an unmodified or a modified phosphodiester internucleoside bridge or a dephospho bridge, preferably phosphorothioate and/or phosphorus diester

and

y independently of one another represents the replacement of a sugar phosphate unit or a β-D-2'-deoxyribose unit, preferably 2'-O-methyl-, 2'-O-propyl- and/or 2'-methoxyethoxyribose or a PNA unit,

where

SEQ ID NO. 40: is 3'- GyGyTyTyTyGxGxGxTxGxGxAxGyGyTyGyG -5',
SEQ ID NO. 41: is 3'- GyGyAyGyGyTxGxGxTxAxCxCxCyCyCyGyG -5',
SEQ ID NO. 42: is 3'- GyGyTxGxGxTxAxCxCxCxCyCyGyG -5',
SEQ ID NO. 43: is 3'- GyGyAyGyGxTxGxGxTxAxCyCyCyC -5',
SEQ ID NO. 44: is 3'- AyGyAyAxAxGxAxAxCxGxAxAxAyGyGyAyA -5',
SEQ ID NO. 45: is 3'- GyGyAxGxGxTxGxGxTxAyCyC -5',
SEQ ID NO. 46: is 3'- GyGyAxGxCxGxAxTxGyGyCyTyTyCyCyA -5',
SEQ ID NO. 47: is 3'- AyAyAyGxGxAxAxCxGxGyGyAyGyCyG -5',
SEQ ID NO. 48: is 3'- GyGyTyCxGxGxTxTxTxGxGyGyTyGyG -5',
SEQ ID NO. 49: is 3'- CyTyTyAxCxAxGxGxTxCxCxGyTyTyGyA -5',
SEQ ID NO. 50: is 3'- GyGyCyCxGxTxGxTxTxCxGyCyTyGyT -5',
SEQ ID NO. 51: is 3'- TyCyAyCxCxCxCxTxCxTxTyTyCyTyGyG -5',
SEQ ID NO. 52: is 3'- GyGyAyCxAxCxCxGxAxCxAyCyGyG -5',
SEQ ID NO. 53: is 3'- AyAyCyGxGxGxAxGxCxGxAyTyGyG -5',
SEQ ID NO. 54: is 3'- AyTyCyTxCxGxGxGxGxTxCxGyTyC -5',
SEQ ID NO. 55: is 3'- AyAyAyGxAxAxCxGxAxAxAxGyGyAyA -5',
SEQ ID NO. 56: is 3'- GyGyTxGxGxTxAxCxCyCyC -5',
SEQ ID NO. 57: is 3'- CyCxCxGxGxTxAxCyTyGyA -5',
SEQ ID NO. 58: is 3'- CyCyAxCxAxGxAxAxAxGyAyAyC -5'

The sequences SEQ ID NO. 40 - SEQ ID NO. 58 correspond to the abovementioned sequences SEQ ID NO. 2 to SEQ ID NO. 20, i.e. they bind to the corresponding sequence sections of a tenascin-coding sequence, where, however, the modifications mentioned are present.

The invention relates to processes for the preparation of the oligonucleotides. The oligonucleotides described can be prepared with the aid of various known, chemical processes, e.g. applying the standard phosphoramidite chemistry using iodine or TED (tetraethylthiuram disulfide) as oxidant. This process is described, for example, in Eckstein, F. (1991) "Oligonucleotides and Analogues, A Practical Approach", IRL Press, Oxford. The oligonucleotides can also be prepared by processes which optionally contain one or more enzymatic steps.

The invention relates to the use of the oligonucleotides. The oligonucleotides can be used for hybridization or binding to tenascin-coding (single-stranded and/or double-stranded) nucleic acids, for example DNA

relates to the use of the oligonucleotides for hybridization with or binding to nucleic acids which have the sequence SEQ ID NO. 1 according to Table 1 or with nucleic acids which have parts of this sequence (for example sequences which code for tenascin isoforms) or with nucleic acids whose sequence differs slightly from these sequences (which have, for example, one or more point mutations).

The invention furthermore relates to the use of the oligonucleotides for the modulation and for the complete or partial inhibition of the expression of tenascin or various tenascin isoforms or of mutants thereof, for example for the complete or partial inhibition of transcription and/or of translation.

The invention relates, for example, to the use of the oligonucleotides as antisense oligonucleotides. Moreover, the oligonucleotides can be used as aids in molecular biology.

The invention furthermore relates to the use of the oligonucleotides as pharmaceutical and/or diagnostic or the use of the oligonucleotides for the production of pharmaceuticals and/or diagnostics. In particular, the oligonucleotides can be employed in pharmaceuticals which are suitable for the prevention and/or treatment of diseases which accompany the expression of an overexpression of tenascin. Since the expression of tenascin is normally, i.e., for example, in the healthy person, limited spatially and temporally, a deviation from this normal spatial and temporal expression can be regarded as overexpression. Furthermore, the oligonucleotides can be employed in diagnostic processes. Such diagnostic processes can be employed, for example, for the diagnosis or early recognition of diseases which accompany abnormal expression (e.g. overexpression) of tenascin.

The invention also relates to a test kit which contains one or more oligonucleotides according to the invention and, if appropriate, further components. Such a test kit can be employed, for example, in diagnosis and as a precaution, for example against skin cancer disorders.

The invention further relates to the use of the oligonucleotides or of pharmaceuticals which contain these oligonucleotides for the treatment of diseases in which tenascin or an overexpression of tenascin is the cause or is involved.

The invention relates in particular to the use of the oligonucleotides or of pharmaceuticals which contain these oligonucleotides for the treatment and/or prevention of diseases in which a dysregulation or disorder of the immigration or of the presence or of the inclusion of melanocytes in epithelial cell layers, for example in the epithelial cell layer of the epidermis, of the choroid membrane of the eye or of the substantia nigra as the basis serves or is involved and of Addison's disease, diabetes mellitus, pernicious anemia and/or thyroid gland dysfunctions.

The invention relates in particular to the use of the oligonucleotides or of pharmaceuticals which contain these oligonucleotides for the treatment and/or prevention of vitiligo and other depigmentation diseases or depigmentation disorders (e.g. of the skin, hair, eyes) for example albinism and/or for the treatment of psoriasis and/or for the treatment of cancer, e.g. for the inhibition of tumor growth and tumor metastasis, for example in melanomas and/or for the treatment of inflammations, in particular as antiinflammatories and/or for the treatment and/or prophylaxis of cardiovascular disorders, for example of restenosis.

In particular, the invention relates to the use of the oligonucleotides for the treatment of vitiligo or for the production of pharmaceuticals which can be used for the treatment of vitiligo. The invention moreover relates quite generally (i.e. also oligonucleotides having a length of greater than or equal to 18 nucleotides) to the use of oligonucleotides for the treatment of vitiligo or the production of pharmaceuticals which can be used for the treatment of vitiligo.

The invention furthermore relates to the use for the treatment of vitiligo in combination with known therapeutic processes, for example in combination a) with photochemotherapy (PUVA), e.g. using methoxypsoralen, phenylalanine and/or khellin and/or b) with the transplantation of cultured melanocytes (epidermal grafting) and/or c) with a steroid treatment and/or d) with a treatment with placenta extracts and/or e) with a treatment with pseudocatalase.

The invention furthermore relates to processes for the production of pharmaceuticals (pharmaceutical preparations). For the production of pharmaceuticals, one or more different oligonucleotides or their

physiologically tolerable salts are mixed, it optionally being possible to add further pharmaceutical vehicles and/or additives.

The invention furthermore relates to pharmaceutical preparations (pharmaceuticals), which contain one or more different oligonucleotides and/or their physiologically tolerable salts, and, if appropriate, pharmaceutical vehicles and/or additives.

The oligonucleotide(s) and/or its/their physiologically tolerable salts can be administered to animals, preferably to mammals, in particular to humans as pharmaceuticals on its/their own, in mixtures with one another or in the form of pharmaceutical preparations. The pharmaceuticals can make possible topical, percutaneous, parenteral and/or enteral administration. The administration form preferred in each case depends on the specific conditions in each case. For the treatment of vitiligo, for example, a topical application, e.g. in the form of ointments, lotions or tinctures, emulsions or suspensions, is preferred. Likewise, the frequency of the administration depends on the individual conditions. For the treatment of vitiligo, for example, a topical composition can be applied to the depigmented skin site one to two times during the day.

As active constituent, pharmaceuticals or pharmaceutical preparations can contain an efficacious dose of at least one oligonucleotide and/or a mixture of a number of oligonucleotides and, if appropriate, additional, pharmaceutically innocuous vehicles and/or additives. Pharmaceutical preparations can contain approximately 0.1% (percent by weight) or less up to approximately 90% (percent by weight) or more of the therapeutically active oligonucleotide or the pharmaceutically active oligonucleotide.

The pharmaceutically efficacious dose of the respective oligonucleotide or of an oligonucleotide which is a constituent of a mixture of various oligonucleotides can vary within wide limits and is to be adapted to the individual conditions in each individual case.

The production of the pharmaceutical preparations can be carried out in a manner known per se, e.g. described in Remingtons Pharmaceutical Sciences (1985), Mack Publ. Co., Easton, PA., it optionally being possible to use pharmaceutically inert inorganic and/or organic vehicles. For the production of pills, tablets, coated tablets and/or hard gelatin capsules, it is

possible to use, for example, lactose, cornstarch and/or derivatives thereof, talc, stearic acid and/or its salts. Vehicles which can be used for soft gelatin capsules and/or suppositories are, for example, fats, waxes, semisolid and/ or liquid polyols, natural and/or hardened oils. Vehicles which can be used for the production of solutions and/or syrups are, for example, water, sucrose, invert sugar, glucose and/or polyols. Vehicles which can be used for the production of injection solutions are, for example, water, alcohols, glycerol, polyols and/or vegetable oils. Vehicles which can be used for microcapsules, implants and/or rods are, for example, copolymers, e.g. of glycolic acid and lactic acid. Moreover, liposome formulations which are known to the person skilled in the art (N. Weiner, Drug Develop Ind Pharm 15 (1989) 1523; "Liposome Dermatics, Springer Verlag 1992), for example HVJ liposomes (Hayashi, Gene Therapy 3 (1996) 878) are suitable. Dermal administration can be carried out, for example, also with the aid of ionophoretic methods and/or with the aid of electroporation. Moreover, lipofectins and/or other (nucleic acid or DNA) carrier systems, for example those which are used in gene therapy, can be used. In particular, suitable systems are those with whose aid oligonucleotides can be introduced into eukaryotic cells or the nuclei of eukaryotic cells with great efficiency.

In addition to the active compounds and vehicles, a pharmaceutical preparation can additionally contain additives, such as, for example, fillers, extenders, disintegrants, binding agents, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings or aromatizers, thickening agents, diluents, buffer substances, furthermore solvents and/or solubilizers and/or agents for achieving a depot effect, and salts for changing the osmotic pressure, coating agents and/or antioxidants. They can also contain two or more different oligonucleotides and/or their physiologically tolerable salts and furthermore, in addition to at least one oligonucleotide, one or more other therapeutically active substances.

Examples

Example 1: Oligonucleotide synthesis

The oligonucleotide was synthesized on an automatic DNA synthesizer (Applied Biosystems Model 380B or 394) using the standard phosphoramidite chemistry and oxidation with iodine (F. Eckstein, Ed

"Oligonucleotides and Analogs, A Practical Approach", IRL Press, Oxford, 1991). For the introduction of phosphorothioate bridges in mixed phosphorothioates and phosphodiester oligonucleotide, oxidation was carried out with TETD (tetraethylthiuram disulfide) instead of iodine (Applied Biosystems User Bulletin 65). After removal of solid carrier (CPG or Tentagel) and removal of the protective groups with conc. NH_3 at 55°C (18 h), the oligonucleotide was first purified by butanol precipitation (Sawadogo, Van Dyke, Nucl. Acids Res. 19 (1991) 674). The sodium salt was then obtained by precipitation from a 0.5 M NaCl solution using 2.5 parts by volume of ethanol.

The oligonucleotide was analyzed with the aid of

a) analytical gel electrophoresis (gel: 20% acrylamide, 8M urea; running buffer: 454M tris borate buffer, pH 7.0) and/or

b) HPLC analysis (column material: Waters GenPak FAX; gradient: CH_3CN (400 ml), H_2O (1.6 l), NaH_2PO_4 (3.1 g), NaCl (11.7 g) pH 6.8 (0.1 M in NaCl) after CH_3CN (400 ml), H_2O (1.6 l), NaH_2PO_4 (3.1 g), NaCl (175.3 g), pH 6.8 (1.5 M in NaCl)) and/or

c) capillary gel electrophoresis (Beckmann capillary eCAP^{TM}, U100P gel column, 65 cm length, 100 mm I.D., window 15 cm from one end; buffer: 140 µM tris, 360 mM boric acid, 7M urea) and/or

d) electrospray mass spectroscopy.

The analysis of the oligonucleotide showed that this was in each case present in a purity of greater than 90%. The methods for the analysis of oligonucleotides are described, for example, in Schweiber and Engler "Analysis of oligonucleotides" (in "Antisense – from technology to therapy", a laboratory manual and textbook, Schlingensiepen et al. eds., Biol. Science, Vol. 6 (1997) p. 78-103).

Synthesized oligonucleotide:

ODN1 (sequence SEQ ID NO. 24): 3'-GsGsAGGTsGGTsACsCsCsC-5'

Example 2: Production of a pharmaceutical preparation

50 mg of ODN 1 from Example 1 can be closely mixed with 1 g of Dermatop® (Hoechst Aktiengesellschaft, Frankfurt am Main, Germany) base cream and the mixture stored at temperatures of <10°C.

Example 3:

The cream from Example 2 can then be applied twice daily (in the morning and afternoon or evening) to a depigmented skin site of a vitiligo patient.

Table 1: Sequence SEQ ID NO. 1:

Sequence of the human tenascin cDNA according to A. Siri et al. Nucl. Acids Res. 19 (1991) 525-531.

```
GAATTCGCTA GAGCCCTAGA GCCCCAGCAG CACCCAGCCA AACCCACCTC CACCATGGGG      60

GCCATGACTC AGCTGTTGGC AGGTGTCTTT CTTGCTTTCC TTGCCCTCGC TACCGAAGGT     120

GGGGTCCTCA AGAAAGTCAT CCGGCACAAG CGACAGAGTG GGGTGAACGC CACCCTGCCA     180

GAAGAGAACC AGCCAGTGGT GTTTAACCAC GTTTACAACA TCAAGCTGCC AGTGGGATCC     240

CAGTGTTCGG TGGATCTGGA GTCAGCCAGT GGGGAGAAAG ACCTGGCACC GCCTTCAGAG     300

CCCAGCGAAA GCTTTCAGGA GCACACAGTA GATGGGGAAA ACCAGATTGT CTTCACACAT     360

CGCATCAACA TCCCCCGCCG GGCCTGTGGC TGTGCCGCAG CCCCTGATGT TAAGGAGCTG     420

CTGAGCAGAC TGGAGGAGCT GGAGAACCTG GTGTCTTCCC TGAGGGAGCA ATGTACTGCA     480

GGAGCAGGCT GCTGTCTCCA GCCTGCCACA GGCCGCTTGG ACACCAGGCC CTTCTGTAGC     540

GGTCGGGGCA ACTTCAGCAC TGAAGGATGT GGCTGTGTCT GCGAACCTGG CTGGAAAGGC     600

CCCAACTGCT CTGAGCCCGA ATGTCCAGGC AACTGTCACC TTCGAGGCCG GTGCATTGAT     660

GGGCAGTGCA TCTGTGACGA CGGCTTCACG GGCGAGGACT GCAGCCAGCT GGCTTGCCCC     720

AGCGACTGCA ATGACCAGGG CAAGTGCGTG AATGGAGTCT GCATCTGTTT CGAAGGCTAC     780

GCGGCTGACT GCAGCCGTGA AATCTGCCCA GTGCCCTGCA GTGAGGAGCA CGGCACATGT     840

GTAGATGGCT TGTGTGTGTG CCACGATGGC TTTGCAGGCG ATGACTGCAA CAAGCCTCTG     900

TGTCTCAACA ATTGCTACAA CCGTGGACGA TGCGTGGAGA ATGAGTGCGT GTGTGATGAG     960

GGTTTCACGG GCGAAGACTG CAGTGAGCTC ATCTGCCCCA ATGACTGCTT CGACCGGGGC    1020

CGCTGCATCA ATGGCACCTG CTACTGCGAA GAAGGCTTCA CAGGTGAAGA CTGCGGGAAA    1080

CCCACCTGCC CACATGCCTG CCACACCCAG GGCCGGTGTG AGGAGGGGCA GTGTGTATGT    1140
```

5

GATGAGGGCT TTGCCGGTGT GGACTGCAGC GAGAAGAGGT GTCCTGCTGA CTGTCACAAT 1200

CGTGGCCGCT GTGTAGACGG GCGGTGTGAG TGTGATGATG GTTTCACTGG AGCTGACTGT 1260

GGGGAGCTCA AGTGTCCCAA TGGCTGCAGT GGCCATGGCC GCTGTGTCAA TGGGCAGTGT 1320

GTGTGTGATG AGGGCTATAC TGGGGAGGAC TGCAGCCAGC TACGGTGCCC CAATGACTGT 1380

CACAGTCGGG GCCGCTGTGT CGAGGGCAAA TGTGTATGTG AGCAAGGCTT CAAGGGCTAT 1440

GACTGCAGTG ACATGAGCTG CCCTAATGAC TGTCACCAGC ACGGCCGCTG TGTGAATGGC 1500

ATGTGTGTTT GTGATGACGG CTACACAGGG GAAGACTGCC GGGATCGCCA ATGCCCCAGG 1560

GACTGCAGCA ACAGGGGCCT CTGTGTGGAC GGACAGTGCG TCTGTGAGGA CGGCTTCACC 1620

GGCCCTGACT GTGCAGAACT CTCCTGTCCA AATGACTGCC ATGGCCAGGG TCGCTGTGTG 1680

AATGGGCAGT GCGTGTGCCA TGAAGGATTT ATGGGCAAAG ACTGCAAGGA GCAAAGATGT 1740

CCCAGTGACT GTCATGGCCA GGGCCGCTGC GTGGACGGCC AGTGCATCTG CCACGAGGGC 1800

TTCACAGGCC TGGACTGTGG CCAGCACTCC TGCCCCAGTG ACTGCAACAA CTTAGGACAA 1860

TGCGTCTCGG GCCGCTGCAT CTGCAACGAG GGCTACAGCG GAGAAGACTG CTCAGAGGTG 1920

TCTCCTCCCA AAGACCTCGT TGTGACAGAA GTGACGGAAG AGACGGTCAA CCTGGCCTGG 1980

GACAATGAGA TGCGGGTCAC AGAGTACCTT GTCGTGTACA CGCCCACCCA CGAGGGTGGT 2040

CTGGAAATGC AGTTCCGTGT GCCTGGGGAC CAGACGTCCA CCATCATCCG GGAGCTGGAG 2100

CCTGGTGTGG AGTACTTTAT CCGTGTATTT GCCATCCTGG AGAACAAGAA GAGCATTCCT 2160

GTCAGCGCCA GGGTGGCCAC GTACTTACCT GCACCTGAAG GCCTGAAATT CAAGTCCATC 2220

AAGGAGACAT CTGTGGAAGT GGAGTGGGAT CCTCTAGACA TTGCTTTTGA AACCTGGGAG 2280

ATCATCTTCC GGAATATGAA TAAAGAAGAT GAGGGAGAGA TCACCAAAAG CCTGAGGAGG 2340

CCAGAGACCT CTTACCGGCA AACTGGTCTA GCTCCTGGGC AAGAGTATGA GATATCTCTG 2400

CACATAGTGA AAAACAATAC CCGGGGCCCT GGCCTGAAGA GGGTGACCAC CACACGCTTG 2460

GATGCCCCCA GCCAGATCGA GGTGAAAGAT GTCACAGACA CCACTGCCTT GATCACCTGG 2520

TTCAAGCCCC TGGCTGAGAT CGATGGCATT GAGCTGACCT ACGGCATCAA AGACGTGCCA 2580

GGAGACCGTA CCACCATCGA TCTCACAGAG GACGAGAACC AGTACTCCAT CGGGAACCTG 2640

AAGCCTGACA CTGAGTACGA GGTGTCCCTC ATCTCCCGCA GAGGTGACAT GTCAAGCAAC 2700

CCAGCCAAAG AGACCTTCAC AACAGGCCTC GATGCTCCCA GGAATCTTCG ACGTGTTTCC 2760

CAGACAGATA ACAGCATCAC CCTGGAATGG AGGAATGGCA AGGCAGCTAT TGACAGTTAC 2820

AGAATTAAGT ATGCCCCCAT CTCTGGAGGG GACCACGCTG AGGTTGATGT TCCAAAGAGC 2880

CAACAAGCCA CAACCAAAAC CACACTCACA GGTCTGAGGC CGGGAACTGA ATATGGGATT 2940

GGAGTTTCTG CTGTGAAGGA AGACAAGGAG AGCAATCCAG CGACCATCAA CGCAGCCACA 3000

GAGTTGGACA CGCCCAAGGA CCTTCAGGTT TCTGAAACTG CAGAGACCAG CCTGACCCTG 3060

CTCTGGAAGA CACCGTTGGC CAAATTTGAC CGCTACCGCC TCAATTACAG TCTCCCCACA 3120

GGCCAGTGGG TGGGAGTGCA GCTTCCAAGA AACACCACTT CCTATGTCCT GAGAGGCCTG 3180

GAACCAGGAC AGGAGTACAA TGTCCTCCTG ACAGCCGAGA AAGGCAGACA CAAGAGCAAG 3240

CCCGCACGTG TGAAGGCATC CACTGAACAA GCCCCTGAGC TGGAAAACCT CACCGTGACT 3300

GAGGTTGGCT GGGATGGCCT CAGACTCAAC TGGACCGCGG CTGACCAGGC CTATGAGCAC 3360

TTTATCATTC AGGTGCAGGA GGCCAACAAG GTGGAGGCAG CTCGGAACCT CACCGTGCCT 3420

GGCAGCCTTC GGGCTGTGGA CATACCGGGC CTCAAGGCTG CTACGCCTTA TACAGTCTCC 3480

ATCTATGGGG TGATCCAGGG CTATAGAACA CCAGTGCTCT CTGCTGAGGC CTCCACAGGG 3540

GAAACTCCCA ATTTGGGAGA GGTCGTGGTG GCCGAGGTGG GCTGGGATGC CCTCAAACTC 3600

AACTGGACTG CTCCAGAAGG GGCCTATGAG TACTTTTTCA TTCAGGTGCA GGAGGCTGAC 3660

ACAGTAGAGG CAGCCCAGAA CCTCACCGTC CCAGGAGGAC TGAGGTCCAC AGACCTGCCT 3720

GGGCTCAAAG CAGCCACTCA TTATACCATC ACCATCCGCG GGTCACTCA GGACTTCAGC 3780

ACAACCCCTC TCTCTGTTGA AGTCTTGACA GAGGAGGTTC CAGATATGGG AAACCTCACA 3840

GTGACCGAGG TTAGCTGGGA TGCTCTCAGA CTGAACTGGA CCACGCCAGA TGGAACCTAT 3900

GACCAGTTTA CTATTCAGGT CCAGGAGGCT GACCAGGTGG AAGAGGCTCA CAATCTCACG 3960

GTTCCTGGCA GCCTGCGTTC CATGGAAATC CCAGGCCTCA GGGCTGGCAC TCCTTACACA 4020

GTCACCCTGC ACGGCGAGGT CAGGGGCCAC AGCACTCGAC CCCTTGCTGT AGAGGTCGTC 4080

CAGTGGGACG TGCCGCTCCA GTCCCCGGTG TCGTGAGCTG GGGAACGACA TCTCCAGCAG 4140

ACAGAGGATC TCCCACAGCT GGGAGATTTA GCCGTGTCTG AGGTTGGCTG GGATGGCCTC 4200

AGACTCAACT GGACCGCAGC TGACAATGCC TATGAGCACT TTGTCATTCA GGTGCAGGAG 4260

GTCAACAAAG TGGAGGCAGC CCAGAACCTC ACGTTGCCTG GCAGCCTCAG GGCTGTGGAC 4320

ATCCCGGGCC TCGAGGCTGC CACGCCTTAT AGAGTCTCCA TCTATGGGGT GATCCGGGGC 4380

TATAGAACAC CAGTACTCTC TGCTGAGGCC TCCACAGCCA AAGAACCTGA AATTGGAAAC 4440

TTAAATGTTT CTGACATAAC TCCCGAGAGC TTCAATCTCT CCTGGATGGC TACCGATGGG 4500

ATCTTCGAGA CCTTTACCAT TGAAATTATT GATTCCAATA GGTTGCTGGA GACTGTGGAA 4560

TATAATATCT CTGGTGCTGA ACGAACTGCC CATATCTCAG GGCTACCCCC TAGTACTGAT 4620

TTTATTGTCT ACCTCTCTGG ACTTGCTCCC AGCATCCGGA CCAAAACCAT CAGTGCCACA 4680

GCCACGACAG AGGCCCTGCC CCTTCTGGAA AACCTAACCA TTTCCGACAT TAATCCCTAC 4740

GGGTTCACAG TTTCCTGGAT GGCATCGGAG AATGCCTTTG ACAGCTTTCT AGTAACGGTG 4800

GTGGATTCTG GGAAGCTGCT GGACCCCCAG GAATTCACAC TTTCAGGAAC CCAGAGGAAG 4860

CTGGAGCTTA GAGGCCTCAT AACTGGCATT GGCTATGAGG TTATGGTCTC TGGCTTCACC 4920

CAAGGGCATC AAACCAAGCC CTTGAGGGCT GAGATTGTTA CAGAAGCCGA ACCGGAAGTT 4980

GACAACCTTC TGGTTTCAGA TGCCACCCCA GACGGTTTCC GTCTGTCCTG GACAGCTGAT 5040

GAAGGGGTCT TCGACAATTT TGTTCTCAAA ATCAGAGATA CCAAAAAGCA GTCTGAGCCA 5100

CTGGAAATAA CCCTACTTGC CCCCGAACGT ACCAGGGACA TAACAGGTCT CAGAGAGGCT 5160

ACTGAATACG AAATTGAACT CTATGGAATA AGCAAAGGAA GGCGATCCCA GACAGTCAGT 5220

GCTATAGCAA CAACAGCCAT GGGCTCCCCA AAGGAAGTCA TTTTCTCAGA CATCACTGAA 5280

AATTCGGCTA CTGTCAGCTG GAGGGCACCC ACGGCCCAAG TGGAGAGCTT CCGGATTACC 5340

TATGTGCCCA TTACAGGAGG TACACCCTCC ATGGTAACTG TGGACGGAAC CAAGACTCAG 5400

ACCAGGCTGG TGAAACTCAT ACCTGGCGTG GAGTACCTTG TCAGCATCAT CGCCATGAAG 5460

GGCTTTGAGG AAAGTGAACC TGTCTCAGGG TCATTCACCA CAGCTCTGGA TGGCCCATCT 5520

GGCCTGGTGA CAGCCAACAT CACTGACTCA GAAGCCTTGG CCAGGTGGCA GCCAGCCATT 5580

GCCACTGTGG ACAGTTATGT CATCTCCTAC ACAGGCGAGA AAGTGCCAGA AATTACACGC 5640

ACGGTGTCCG GGAACACAGT GGAGTATGCT CTGACCGACC TCGAGCCTGC CACGGAATAC 5700

ACACTGAGAA TCTTTGCAGA GAAAGGGCCC CAGAAGAGCT CAACCATCAC TGCCAAGTTC 5760

ACAACAGACC TCGATTCTCC AAGAGACTTG ACTGCTACTG AGGTTCAGTC GGAAACTGCC 5820

CTCCTTACCT GGCGACCCCC CCGGGCATCA GTCACCGGTT ACCTGCTGGT CTATGAATCA 5880

GTGGATGGCA CAGTCAAGGA AGTCATTGTG GGTCCAGATA CCACCTCCTA CAGCCTGGCA 5940

GACCTGAGCC CATCCACCCA CTACACAGCC AAGATCCAGG CACTCAATGG GCCCCTGAGG 6000

AGCAATATGA TCCAGACCAT CTTCACCACA ATTGGACTCC TGTACCCCTT CCCCAAGGAC 6060

TGCTCCCAAG CAATGCTGAA TGGAGACACG ACCTCTGGCC TCTACACCAT TTATCTGAAT 6120

GGTGATAAGG CTCAGGCGCT GGAAGTCTTC TGTGACATGA CCTCTGATGG GGGTGGATGG 6180

ATTGTGTTCC TGAGACGCAA AAACGGACGC GAGAACTTCT ACCAAAACTG GAAGGCATAT 6240

GCTGCTGGAT TTGGGGACCG CAGAGAAGAA TTCTGGCTTG GCTGGACAA CCTGAACAAA 6300

ATCACAGCCC AGGGGCAGTA CGAGCTCCGG GTGGACCTGC GGGACCATGG GGAGACAGCC 6360

TTTGCTGTCT ATGACAAGTT CAGCGTGGGA GATGCCAAGA CTCGCTACAA GCTGAAGGTG 6420

GAGGGGTACA GTGGGACAGC AGGTGACTCC ATGGCCTACC ACAATGGCAG ATCCTTCTCC 6480

ACCTTTGACA AGGACACAGA TTCAGCCATC ACCAACTGTG CTCTGTCTAC AAGGGGCTTC 6540

TGGTACAGGA ACTGTCACCG TGTCAACCTG ATGGGGAGAT ATGGGGACAA TAACCACAGT 6600

CAGGGCGTTA ACTGGTTCCA CTGGAAGGGC CACGAACACT CAATCCAGTT TGCTGAGATG 6660

AAGCTGAGAC CAAGCAACTT CAGAAATCTT GAAGGCAGGC GCAAACGGGC ATAAATTGGA 6720

GGGACCACTG GGTGAGAGAG GAATAAGGCG GCCCAGAGCG AGGAAAGGAT TTTACCAAAG 6780

CATCAATACA ACCAGCCCAA CCATCGGTCC ACACCTGGGC ATTTGGTGAG AATCAAAGCT 6840

GACCATGGAT CCCTGGGGCC AACGGCAACA GCATGGGCCT CACCTCCTCT GTGATTTCTT 6900

TCTTTGCACC AAAGACATCA GTCTCCAACA TGTTTCTGTT TTGTTGTTTG ATTCAGCAAA 6960

AATCTCCCAG TGACAACATC GCAATAGTTT TTTACTTCTC TTAGGTGGCT CTGGGATGGG 7020

AGAGGGGTAG GATGTACAGG GGTAGTTTGT TTTAGAACCA GCCGTATTTT ACATGAAGCT 7080

GTATAATTAA TTGTCATTAT TTTTGTTAGC AAAGATTAAA TGTGTCATTG GAAGCCATCC 7140

CTTTTTTTAC ATTTCATACA ACAGAAACCA GAAAAGCAAT ACTGTTTCCA TTTTAAGGAT 7200

ATGATTAATA TTATTAATAT AATAATGATG ATGATGATGA TGAAAACTAA GGATTTTTCA 7260

AGAGATCTTT CTTTCCAAAA CATTTCTGGA CAGTACCTGA TTGTATTTTT TTTTTAAATA 7320

AAAGCACAAG TACTTTTGAA AAAAAA 7346

Patent claims:

1. An oligonucleotide which binds to a nucleic acid which codes for one of the isoforms of human tenascin or parts thereof and inhibits its expression, where the oligonucleotide has a length of 7 to 15 nucleotide units and where the oligonucleotide can optionally be modified, and the physiologically tolerable salts of the oligonucleotide.

2. The oligonucleotide as claimed in claim 1, in which the oligonucleotide binds to a region of the nucleic acid which comprises

a) a part of the 5'-noncoding region and/or
the translation start or

b) the translation start and/or
a part of the coding region or

c) a part of the coding region and/or
a part of the 3'-noncoding region.

3. The oligonucleotide as claimed in claim 1, in which the oligonucleotide has one of the sequences SEQ ID NO. 2 to SEQ ID NO. 20, where SEQ ID NO. 2 to SEQ ID NO. 20 have the following meaning:

SEQ. ID NO. 2: 3'- GGTTTGGGTGGAGGTGG -5'
SEQ. ID NO. 3: 3'- GGAGGTGGTACCCCCGG -5'
SEQ. ID NO. 4: 3'- GGTGGTACCCCCGG -5'
SEQ. ID NO. 5: 3'- GGAGGTGGTACCCC -5'
SEQ. ID NO. 6: 3'- AGAAAGAACGAAAGGAA -5'
SEQ. ID NO. 7: 3'- GGAGGTGGTACC -5'
SEQ. ID NO. 8: 3'- GGAGCGATGGCTTCCA -5'
SEQ. ID NO. 9: 3'- AAAGGAACGGGAGCG -5'
SEQ. ID NO. 10: 3'- GGTCGGTTTGGGTGG -5'

SEQ. ID NO. 11: 3'- CTTACAGGTCCGTTGA -5'

SEQ. ID NO. 12: 3'- GGCCGTGTTCGCTGT -5'

SEQ. ID NO. 13: 3'- TCACCCCTCTTTCTGG -5'

SEQ. ID NO. 14: 3'- GGACACCGACACGG -5'

SEQ. ID NO. 15: 3'- AACGGGAGCGATGG -5'

SEQ. ID NO. 16: 3'- ATCTCGGGGTCGTC -5'

SEQ. ID NO. 17: 3'- AAAGAACGAAAGGAA -5'

SEQ. ID NO. 18: 3'- GGTGGTACCCC -5'

SEQ. ID NO. 19: 3'- CCCGGTACTGA -5'

SEQ. ID NO. 20: 3'- CCACAGAAAGAAC -5'

4. The oligonucleotide as claimed in one or more of claims 1 to 3, in which the oligonucleotide has one or more modifications which are located on certain nucleoside positions and/or internucleoside bridges.

5. The oligonucleotide as claimed in one or more of claims 1 to 4, in which the chemical modifications can be selected independently of one another from the group consisting of the chemical modifications a) to h):

a) the replacement of a phosphoric acid diester internucleoside bridge by a modified phospho bridge,

b) the replacement of a phosphoric acid diester internucleoside bridge by a "dephospho" bridge,

c) the replacement of a sugar phosphate unit by another unit,

d) the replacement of a β-D-2'-deoxyribose unit by a modified sugar unit,

e) the modification or the replacement of a natural nucleoside base by a modified nucleoside base,

f) the conjugation of the oligonucleotide to a molecule which adapts the properties of the oligonucleotide to a specific requirement,

g) the conjugation of the oligonucleotide to a 2'5-bonded oligoadenylate or a derivative thereof, the conjugation of the 2'5'-bonded oligoadenylate or a derivative thereof optionally taking place via a linker,

and

h) the introduction of a 3'-3' inversion and/or 5'-5' inversion at the 3' or 5' end of the oligonucleotide.

6. The oligonucleotide as claimed in one or more of claims 1 to 5, the oligonucleotide containing one or more chemical modifications which can be selected independently of one another from the group consisting of the chemical modifications a) to h):

a) the replacement of a phosphoric acid diester internucleoside bridge by a modified phospho bridge,

where a modified phospho bridge is a phosphorothioate, phosphorodithioate, $NR^1R^{1'}$-phosphoramidate, boranophosphate, phosphate-(C_1-C_{21})-O-alkyl ester, phosphate-[(C_6-C_{12})aryl-(C_1-C_{21})-O-alkyl] ester, (C_1-C_8)alkylphosphonate or (C_6-C_{12})-arylphosphonate bridge,

where

R^1 and $R^{1'}$ independently of one another are selected from the group comprising hydrogen, (C_1-C_{18})-alkyl, (C_6-C_{20})-aryl, (C_6-C_{14})-aryl-(C_1-C_8)-alkyl or

R^1 and $R^{1'}$ together with the nitrogen atom carrying them, form a 5- to 6-membered heterocyclic ring which can additionally contain a further heteroatom from the group consisting of O, S and N;

b) the replacement of a phosphoric acid diester internucleoside bridge by a "dephospho" bridge,

where a "dephospho bridge" is a formacetal, 3'-thioformacetal, methylhydroxylamine, oxime, methylenedimethylhydrazo, dimethylenesulfone or silyl bridge,

c) the complete or partial replacement of the sugar phosphate backbone (replacement of sugar phosphate units) by other units,

where another unit is suitable for synthesizing a "morpholine derivative" oligomer, a polyamide nucleic acid ("PNA") or a phosphomonoacid ester nucleic acid,

d) the replacement of a β-D-2'-deoxyribose unit by a modified sugar unit,

where a modified sugar unit is an α-D-2'-deoxyribose, L-2'-deoxyribose, 2'-F-2'-deoxyribose, 2'-O-(C_1-C_6)alkylribose, 2'-O-(C_2-C_6)alkenylribose, 2'-[O-(C_1-C_6)alkyl-O-(C_1-C_6)alkyl]ribose, 2'-NH_2-2'-deoxyribose, β-D-xylofuranose, α-arabinofuranose, 2,4-dideoxy-β-D-erythro-hexopyranose, a carbocyclic sugar analog, an open-chain sugar analog or a bicyclo sugar analog,

e) the replacement of a natural nucleoside base by a modified nucleoside base,

where a modified nucleoside base is 5-(hydroxymethyl)uracil, 5-aminouracil, pseudouracil, dihydrouracil, 5-(C_1-C_6-alkyluracil, 5-(C_2-C_6)-alkenyluracil, 5-(C_2-C_6)-alkynyluracil, 5-(C_1-C_6)-alkylcytosine, 5-(C_2-C_6)-alkenylcytosine, 5-(C_2-C_6)-alkynylcytosine, 5-fluorouracil, 5-fluorocytosine, 5-chlorouracil, 5-chlorocytosine, 5-bromouracil, 5-

bromocytosine, a 7-deaza-7-substituted purine, or a 7-deaza-8-substituted purine,

f) conjugation to a molecule,

where the molecule is a polylysine, intercalator, fluorescent molecule, crosslinker, lipophilic molecule, lipid, steroid, vitamin, polyethylene glycol, oligoethylene glycol, (C_{12}-C_{18})-alkyl phosphate diester or –O-CH_2-CH(OH)-O-(C_{12}-C_{18})-alkyl group,

g) conjugation to a 2'5'-linked oligoadenylate or a derivative thereof

where a 2'5'-linked oligoadenylate or a derivative thereof is a 2'5'-linked triadenylate, 2'5'-linked tetraadenylate, 2'5'-linked pentaadenylate or cordycepin (2'5'-linked 3'-deoxyadenylate),

where the conjugation optionally takes place via a linker and

where the 5' end of the 2'5'-linked oligoadenylate optionally contains a phosphate, diphosphate or triphosphate group and

h) the introduction of a 3'-3' and/or 5'-5' inversion at the 3'- and/or at the 5'-end of the oligonucleotide.

7. The oligonucleotide as claimed in one or more of claims 1 to 6, in which either a) only certain phosphodiester internucleoside bridges or

b) all phosphodiester internucleoside bridges

are modified.

8. The oligonucleotide as claimed in one or more of claims 1 to 7, in which 1 – 5 terminal internucleoside bridges are modified at the 5- and/or at the 3'- end of the oligonucleotide.

9. The oligonucleotide as claimed in one or more of claims 1 to 8, in which the internucleoside bridges located at the 3'- and/or 5'- end of nonterminal nucleosides which contain a pyrimidine base are modified.

10. The oligonucleotide as claimed in one or more of claims 1 to 9, in which the oligonucleotide has a sequence selected from the group consisting of the sequences SEQ ID NO. 21 to SEQ ID NO. 39, the sequences SEQ ID NO. 21 to SEQ ID NO. 39 having the following meaning:

SEQ ID NO. 21: 3'- GsGsTsTsTGGGTsGGAGGsTsGsG -5',
SEQ ID NO. 22: 3'- GsGsAsGGTsGGTsACsCCsCCsGsG -5',
SEQ ID NO. 23: 3'- GsGsTGGTsACsCsCCsCsGsG -5',
SEQ ID NO. 24: 3'- GsGsAGGTsGGTsACsCsCsC -5',
SEQ ID NO. 25: 3'- AsGsAAAGAAsCsGAAAGGsAsA -5',
SEQ ID NO. 26: 3'- GsGsAGGTsGGTsAsCsC -5',
SEQ ID NO. 27: 3'- GsGsAGCsGATsGGCsTsTsCsCsA -5',
SEQ ID NO. 28: 3'- AsAsAGGAACsGGGAGsCsG -5',
SEQ ID NO. 29: 3'- GsGsTCGGTsTsTGGGTsGsG -5',
SEQ ID NO. 30: 3'- CsTsTACAGGTsCsCGTsTsGsA -5',
SEQ ID NO. 31: 3'- GsGsCsCGsTGTsTCGCsTsGsT -5',
SEQ ID NO. 32: 3'- TsCsACsCCsCTsCsTTsTsCsTsGsG -5',
SEQ ID NO. 33: 3'- GsGsAsCACsCGACsACsGsG -5',
SEQ ID NO. 34: 3'- AsAsCsGGGAGCGATsGsG -5',
SEQ ID NO. 35: 3'- AsTsCsTCGGGGTsCsGsTsC -5',
SEQ ID NO. 36: 3'- AsAsAGAACsGAAAGGsAsA -5',
SEQ ID NO. 37: 3'- GsGsTGGTsACsCsCsC -5',
SEQ ID NO. 38: 3'- CsCsCsGGTsACsTsGsA -5' and
SEQ ID NO. 39: 3'- CsCsAsCAGAAAGsAsAsC -5',

where "s" indicates the position of a modified internucleoside bridge.

11. The oligonucleotide as claimed in one or more of claims 1 to 8, where the oligonucleotide has one of the sequences SEQ ID NO. 40 to SEQ ID NO. 58, the sequences SEQ ID NO. 40 to SEQ ID NO. 58 having the following meaning

SEQ ID NO. 40: 3'- GyGyTyTyTyGxGxGxTxGxGxAxGyGyTyGyG -5',

SEQ ID NO. 41: 3'- GyGyAyGyGyTxGxGxTxAxCxCxCyCyCyGyG -5',

SEQ ID NO. 42: 3'- GyGyTxGxGxTxAxCxCxCxCyCyGyG -5',

SEQ ID NO. 43: 3'- GyGyAyGyGxTxGxGxTxAxCyCyCyC -5',

SEQ ID NO. 44: 3'- AyGyAyAxAxGxAxAxCxGxAxAxAyGyGyAyA -5',

SEQ ID NO. 45: 3'- GyGyAxGxGxTxGxGxTxAyCyC -5',

SEQ ID NO. 46: 3'- GyGyAxGxCxGxAxTxGyGyCyTyTyCyCyA -5',

SEQ ID NO. 47: 3'- AyAyAyGxGxAxAxCxGxGyGyAyGyCyG -5',

SEQ ID NO. 48: 3'- GyGyTyCxGxGxTxTxTxGxGyGyTyGyG -5',

SEQ ID NO. 49: 3'- CyTyTyAxCxAxGxGxTxCxCxGyTyTyGyA -5',

SEQ ID NO. 50: 3'- GyGyCyCxGxTxGxTxTxCxGyCyTyGyT -5',

SEQ ID NO. 51: 3'- TyCyAyCxCxCxCxTxCxTxTyTyCyTyGyG -5',

SEQ ID NO. 52: 3'- GyGyAyCxAxCxCxGxAxCxAyCyGyG -5',

SEQ ID NO. 53: 3'- AyAyCyGxGxGxAxGxCxGxAyTyGyG -5',

SEQ ID NO. 54: 3'- AyTyCyTxCxGxGxGxGxTxCxGyTyC -5',

SEQ ID NO. 55: 3'- AyAyAyGxAxAxCxGxAxAxAxGyGyAyA -5',

SEQ ID NO. 56: 3'- GyGyTxGxGxTxAxCxCyCyC -5',

SEQ ID NO. 57: 3'- CyCxCxGxGxTxAxCyTyGyA -5' and

SEQ ID NO. 58: 3'- CyCyAxCxAxGxAxAxAxGyAyAyC -5',

where

"x" independently of one another represents a phosphodiester internucleoside bridge or a modified internucleoside bridge and

"y" independently of one another represents the replacement of a sugar phosphate unit or of a β-D-2'-deoxyribose unit, the modified β-D-2'-deoxyribose unit being located at the 3'- end of "y".

12. The oligonucleotide as claimed in claim 11, where "y" represents 2'-O-methyl-, 2'-O-propyl- or 2'-methoxyethoxyribose or a PNA unit.

13. The use of an oligonucleotide as claimed in one or more of claims 1 to 12 for the inhibition of the expression of tenascin.

14. The use of an oligonucleotide as claimed in one or more of claims 1 to 12 as a tool in molecular biology.

15. The use of an oligonucleotide as claimed in one or more of claims 1 to 12 as a diagnostic.

16. The use of an oligonucleotide as claimed in one or more of claims 1 to 12 as a pharmaceutical.

17. The use of an oligonucleotide as claimed in one or more of claims 1 to 12 for the production of a pharmaceutical.

18. A pharmaceutical comprising one or more oligonucleotides as claimed in one or more of claims 1 to 12 and, if appropriate, one or more pharmaceutical vehicles and/or additives.

19. The use of a pharmaceutical as claimed in claim 18 in combination with photochemotherapy and/or the transplantation of cultured melanocytes and/or treatment with steroids and/or treatment with placenta extracts.

20. A process for the production of a pharmaceutical, an efficacious dose of one or more oligonucleotides as claimed in one or more of claims 1 to 12 being mixed with one or more pharmaceutical vehicles and/or additives.

21. A process for the preparation of an oligonucleotide as claimed in one or more of claims 1 to 12, the oligonucleotide being chemically synthesized on a solid phase.

22. A diagnostic comprising one or more oligonucleotides as claimed in one or more of claims 1 to 12.

23. A test kit comprising one or more oligonucleotides as claimed in one or more of claims 1 to 12.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY

As below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below, I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Antisense oligonucleotides against tenascin for the treating of vitiligo

the specification of which

was filed on October 29, 1998 as International Patent Application PCT/EP98/06868.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s) for which Priority is Claimed:

Federal Republic of Germany, 19750702.6-44 of NOVEMBER 15, 1997

And I hereby appoint
Douglas B. Henderson, Reg.No. 20,291; Arthur S. Garrett, Reg.No. 20,338
Jerry D. Voight, Reg.No. 23,020; Herbert H. Mintz, Reg.No. 26,691;
Thomas L. Irving, Reg.No. 28,619; Thomas W. Winland, Reg.No. 27,605;
Martin I. Fuchs, Reg.No. 28,805; Susan H. Griffen, Reg.No. 30,907;
Richard B. Racine, Reg.No. 30,415; Thomas H. Jenkins, Reg.No. 30,857;
Carol P. Einaudi, Reg.No. 32,226; Frank E. Caffoe, Reg.No. 18,621;
Allen R. Jensen, Reg.No. 28,224; Bryan C. Diner, Reg.No. 32,409;
M. Paul Barker, Reg.No. 32,013; Charles E. Van Horn, Reg.No. 40,266;
David S. Forman, Reg.No. 33,694;
all of the firm of FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, Reg.No. 22,540, my attorneys, with full power of substitution and revocation to prosecute this application, to make alterations and amendments therein, to file continuation and divisional applications thereof, to receive the Patent, and to transact all business in the Patent and Trademark Office and in the Courts in connection therein, and specify that communications about the application are to be directed to the following correspondence address:

FINNEGAN, HENDERSON, FARABOW, GARRETT AND DUNNER
Franklin Square Bldg., Suite 700
1300 I Street, N.W.
Washington, DC 20005-3315
Tel. 202-408-4000

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

INVENTOR(S) / Residence

1 - 00 1) Dr. Anuschirwan Peyman, Zeilsheimer Straße 46, 65779 Kelkheim, Germany DEX

Signature: Anuschirwan Peyman Date: 23.5.2000

2 - 00 2) Dr. Eugen Uhlmann, Zum Talblick 31, 61479 Glashütten, Germany DEX

Signature: Eugen Uhlmann Date: 23.5.2000

3 - 00 3) Caroline Weiser, Karl-Staib-Straße 37, 65795 Hattersheim, Germany DEX

Signature: Caroline Weiser Date: 09.06.2000

The inventors are citizens of **Germany**.

Post Office Address of all Inventors:

Aventis Pharma Deutschland GmbH
Patent- und Lizenzabteilung
Industriepark Höchst, Geb. K 801
65926 Frankfurt
Germany

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT:
(A) NAME: Hoechst Marion Roussel Deutschland GmbH
(B) STREET: -
(C) CITY: Frankfurt
(D) STATE: -
(E) COUNTRY: Germany
(F) POSTAL CODE (ZIP): 65926
(G) TELEPHONE: 069-305-7072
(H) TELEFAX: 069-35-7175
(I) TELEX: -

(ii) TITLE OF INVENTION: Antisense Oligonukleotide gegen Tenascin zur Behandlung von Vitiligo

(iii) NUMBER OF SEQUENCES: 58

(iv) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30 (EPO)

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7346 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..7346

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
GAATTCGCTA GAGCCCTAGA GCCCCAGCAG CACCCAGCCA AACCCACCTC CACCATGGGG      60
GCCATGACTC AGCTGTTGGC AGGTGTCTTT CTTGCTTTCC TTGCCCTCGC TACCGAAGGT     120
GGGGTCCTCA AGAAAGTCAT CCGGCACAAG CGACAGAGTG GGGTGAACGC CACCCTGCCA     180
GAAGAGAACC AGCCAGTGGT GTTTAACCAC GTTTACAACA TCAAGCTGCC AGTGGGATCC     240
CAGTGTTCGG TGGATCTGGA GTCAGCCAGT GGGGAGAAAG ACCTGGCACC GCCTTCAGAG     300
CCCAGCGAAA GCTTTCAGGA GCACACAGTA GATGGGGAAA ACCAGATTGT CTTCACACAT     360
CGCATCAACA TCCCCCGCCG GGCCTGTGGC TGTGCCGCAG CCCCTGATGT TAAGGAGCTG     420
CTGAGCAGAC TGGAGGAGCT GGAGAACCTG GTGTCTTCCC TGAGGGAGCA ATGTACTGCA     480
GGAGCAGGCT GCTGTCTCCA GCCTGCCACA GGCCGCTTGG ACACCAGGCC CTTCTGTAGC     540
GGTCGGGGCA ACTTCAGCAC TGAAGGATGT GGCTGTGTCT GCGAACCTGG CTGGAAAGGC     600
CCCAACTGCT CTGAGCCCGA ATGTCCAGGC AACTGTCACC TTCGAGGCCG GTGCATTGAT     660
GGGCAGTGCA TCTGTGACGA CGGCTTCACG GGCGAGGACT GCAGCCAGCT GGCTTGCCCC     720
AGCGACTGCA ATGACCAGGG CAAGTGCGTG AATGGAGTCT GCATCTGTTT CGAAGGCTAC     780
GCGGCTGACT GCAGCCGTGA AATCTGCCCA GTGCCCTGCA GTGAGGAGCA CGGCACATGT     840
GTAGATGGCT TGTGTGTGTG CCACGATGGC TTTGCAGGCG ATGACTGCAA CAAGCCTCTG     900
TGTCTCAACA ATTGCTACAA CCGTGGACGA TGCGTGGAGA ATGAGTGCGT GTGTGATGAG     960
```

GGTTTCACGG GCGAAGACTG CAGTGAGCTC ATCTGCCCCA ATGACTGCTT CGACCGGGGC 1020
CGCTGCATCA ATGGCACCTG CTACTGCGAA GAAGGCTTCA CAGGTGAAGA CTGCGGGAAA 1080
CCCACCTGCC CACATGCCTG CCACACCCAG GGCCGGTGTG AGGAGGGGCA GTGTGTATGT 1140
GATGAGGGCT TTGCCGGTGT GGACTGCAGC GAGAAGAGGT GTCCTGCTGA CTGTCACAAT 1200
CGTGGCCGCT GTGTAGACGG GCGGTGTGAG TGTGATGATG GTTTCACTGG AGCTGACTGT 1260
GGGGAGCTCA AGTGTCCCAA TGGCTGCAGT GGCCATGGCC GCTGTGTCAA TGGGCAGTGT 1320
GTGTGTGATG AGGGCTATAC TGGGGAGGAC TGCAGCCAGC TACGGTGCCC CAATGACTGT 1380
CACAGTCGGG GCCGCTGTGT CGAGGGCAAA TGTGTATGTG AGCAAGGCTT CAAGGGCTAT 1440
GACTGCAGTG ACATGAGCTG CCCTAATGAC TGTCACCAGC ACGGCCGCTG TGTGAATGGC 1500
ATGTGTGTTT GTGATGACGG CTACACAGGG GAAGACTGCC GGGATCGCCA ATGCCCCAGG 1560
GACTGCAGCA ACAGGGGCCT CTGTGTGGAC GGACAGTGCG TCTGTGAGGA CGGCTTCACC 1620
GGCCCTGACT GTGCAGAACT CTCCTGTCCA AATGACTGCC ATGGCCAGGG TCGCTGTGTG 1680
AATGGGCAGT GCGTGTGCCA TGAAGGATTT ATGGGCAAAG ACTGCAAGGA GCAAAGATGT 1740
CCCAGTGACT GTCATGGCCA GGGCCGCTGC GTGGACGGCC AGTGCATCTG CCACGAGGGC 1800
TTCACAGGCC TGGACTGTGG CCAGCACTCC TGCCCCAGTG ACTGCAACAA CTTAGGACAA 1860
TGCGTCTCGG GCCGCTGCAT CTGCAACGAG GGCTACAGCG GAGAAGACTG CTCAGAGGTG 1920
TCTCCTCCCA AAGACCTCGT TGTGACAGAA GTGACGGAAG AGACGGTCAA CCTGGCCTGG 1980
GACAATGAGA TGCGGGTCAC AGAGTACCTT GTCGTGTACA CGCCCACCCA CGAGGGTGGT 2040
CTGGAAATGC AGTTCCGTGT GCCTGGGGAC CAGACGTCCA CCATCATCCG GGAGCTGGAG 2100
CCTGGTGTGG AGTACTTTAT CCGTGTATTT GCCATCCTGG AGAACAAGAA GAGCATTCCT 2160
GTCAGCGCCA GGGTGGCCAC GTACTTACCT GCACCTGAAG GCCTGAAATT CAAGTCCATC 2220
AAGGAGACAT CTGTGGAAGT GGAGTGGGAT CCTCTAGACA TTGCTTTTGA AACCTGGGAG 2280
ATCATCTTCC GGAATATGAA TAAAGAAGAT GAGGGAGAGA TCACCAAAAG CCTGAGGAGG 2340
CCAGAGACCT CTTACCGGCA AACTGGTCTA GCTCCTGGGC AAGAGTATGA GATATCTCTG 2400
CACATAGTGA AAAACAATAC CCGGGGCCCT GGCCTGAAGA GGGTGACCAC CACACGCTTG 2460
GATGCCCCCA GCCAGATCGA GGTGAAAGAT GTCACAGACA CCACTGCCTT GATCACCTGG 2520
TTCAAGCCCC TGGCTGAGAT CGATGGCATT GAGCTGACCT ACGGCATCAA AGACGTGCCA 2580
GGAGACCGTA CCACCATCGA TCTCACAGAG GACGAGAACC AGTACTCCAT CGGGAACCTG 2640
AAGCCTGACA CTGAGTACGA GGTGTCCCTC ATCTCCCGCA GAGGTGACAT GTCAAGCAAC 2700
CCAGCCAAAG AGACCTTCAC AACAGGCCTC GATGCTCCCA GGAATCTTCG ACGTGTTTCC 2760
CAGACAGATA ACAGCATCAC CCTGGAATGG AGGAATGGCA AGGCAGCTAT TGACAGTTAC 2820
AGAATTAAGT ATGCCCCCAT CTCTGGAGGG GACCACGCTG AGGTTGATGT TCCAAAGAGC 2880
CAACAAGCCA CAACCAAAAC CACACTCACA GGTCTGAGGC CGGGAACTGA ATATGGGATT 2940
GGAGTTTCTG CTGTGAAGGA AGACAAGGAG AGCAATCCAG CGACCATCAA CGCAGCCACA 3000
GAGTTGGACA CGCCCAAGGA CCTTCAGGTT TCTGAAACTG CAGAGACCAG CCTGACCCTG 3060
CTCTGGAAGA CACCGTTGGC CAAATTTGAC CGCTACCGCC TCAATTACAG TCTCCCCACA 3120
GGCCAGTGGG TGGGAGTGCA GCTTCCAAGA AACACCACTT CCTATGTCCT GAGAGGCCTG 3180
GAACCAGGAC AGGAGTACAA TGTCCTCCTG ACAGCCGAGA AAGGCAGACA CAAGAGCAAG 3240
CCCGCACGTG TGAAGGCATC CACTGAACAA GCCCCTGAGC TGGAAAACCT CACCGTGACT 3300
GAGGTTGGCT GGGATGGCCT CAGACTCAAC TGGACCGCGG CTGACCAGGC CTATGAGCAC 3360
TTTATCATTC AGGTGCAGGA GGCCAACAAG GTGGAGGCAG CTCGGAACCT CACCGTGCCT 3420
GGCAGCCTTC GGGCTGTGGA CATACCGGGC CTCAAGGCTG CTACGCCTTA TACAGTCTCC 3480
ATCTATGGGG TGATCCAGGG CTATAGAACA CCAGTGCTCT CTGCTGAGGC CTCCACAGGG 3540
GAAACTCCCA ATTTGGGAGA GGTCGTGGTG GCCGAGGTGG GCTGGGATGC CCTCAAACTC 3600
AACTGGACTG CTCCAGAAGG GGCCTATGAG TACTTTTTCA TTCAGGTGCA GGAGGCTGAC 3660
ACAGTAGAGG CAGCCCAGAA CCTCACCGTC CCAGGAGGAC TGAGGTCCAC AGACCTGCCT 3720
GGGCTCAAAG CAGCCACTCA TTATACCATC ACCATCCGCG GGGTCACTCA GGACTTCAGC 3780
ACAACCCCTC TCTCTGTTGA AGTCTTGACA GAGGAGGTTC CAGATATGGG AAACCTCACA 3840
GTGACCGAGG TTAGCTGGGA TGCTCTCAGA CTGAACTGGA CCACGCCAGA TGGAACCTAT 3900
GACCAGTTTA CTATTCAGGT CCAGGAGGCT GACCAGGTGG AAGAGGCTCA CAATCTCACG 3960
GTTCCTGGCA GCCTGCGTTC CATGGAAATC CCAGGCCTCA GGGCTGGCAC TCCTTACACA 4020
GTCACCCTGC ACGGCGAGGT CAGGGGCCAC AGCACTCGAC CCCTTGCTGT AGAGGTCGTC 4080
CAGTGGGACG TGCCGCTCCA GTCCCCGGTG TCGTGAGCTG GGGAACGACA TCTCCAGCAG 4140
ACAGAGGATC TCCCACAGCT GGGAGATTTA GCCGTGTCTG AGGTTGGCTG GGATGGCCTC 4200
AGACTCAACT GGACCGCAGC TGACAATGCC TATGAGCACT TTGTCATTCA GGTGCAGGAG 4260
GTCAACAAAG TGGAGGCAGC CCAGAACCTC ACGTTGCCTG GCAGCCTCAG GGCTGTGGAC 4320
ATCCCGGGCC TCGAGGCTGC CACGCCTTAT AGAGTCTCCA TCTATGGGGT GATCCGGGGC 4380
TATAGAACAC CAGTACTCTC TGCTGAGGCC TCCACAGCCA AAGAACCTGA AATTGGAAAC 4440
TTAAATGTTT CTGACATAAC TCCCGAGAGC TTCAATCTCT CCTGGATGGC TACCGATGGG 4500
ATCTTCGAGA CCTTTACCAT TGAAATTATT GATTCCAATA GGTTGCTGGA GACTGTGGAA 4560

TATAATATCT CTGGTGCTGA ACGAACTGCC CATATCTCAG GGCTACCCCC TAGTACTGAT 4620
TTTATTGTCT ACCTCTCTGG ACTTGCTCCC AGCATCCGGA CCAAAACCAT CAGTGCCACA 4680
GCCACGACAG AGGCCCTGCC CCTTCTGGAA AACCTAACCA TTTCCGACAT TAATCCCTAC 4740
GGGTTCACAG TTTCCTGGAT GGCATCGGAG AATGCCTTTG ACAGCTTTCT AGTAACGGTG 4800
GTGGATTCTG GGAAGCTGCT GGACCCCCAG GAATTCACAC TTTCAGGAAC CCAGAGGAAG 4860
CTGGAGCTTA GAGGCCTCAT AACTGGCATT GGCTATGAGG TTATGGTCTC TGGCTTCACC 4920
CAAGGGCATC AAACCAAGCC CTTGAGGGCT GAGATTGTTA CAGAAGCCGA ACCGGAAGTT 4980
GACAACCTTC TGGTTTCAGA TGCCACCCCA GACGGTTTCC GTCTGTCCTG GACAGCTGAT 5040
GAAGGGGTCT TCGACAATTT TGTTCTCAAA ATCAGAGATA CCAAAAAGCA GTCTGAGCCA 5100
CTGGAAATAA CCCTACTTGC CCCCGAACGT ACCAGGGACA TAACAGGTCT CAGAGAGGCT 5160
ACTGAATACG AAATTGAACT CTATGGAATA AGCAAAGGAA GGCGATCCCA GACAGTCAGT 5220
GCTATAGCAA CAACAGCCAT GGGCTCCCCA AAGGAAGTCA TTTTCTCAGA CATCACTGAA 5280
AATTCGGCTA CTGTCAGCTG GAGGGCACCC ACGGCCCAAG TGGAGAGCTT CCGGATTACC 5340
TATGTGCCCA TTACAGGAGG TACACCCTCC ATGGTAACTG TGGACGGAAC CAAGACTCAG 5400
ACCAGGCTGG TGAAACTCAT ACCTGGCGTG GAGTACCTTG TCAGCATCAT CGCCATGAAG 5460
GGCTTTGAGG AAAGTGAACC TGTCTCAGGG TCATTCACCA CAGCTCTGGA TGGCCCATCT 5520
GGCCTGGTGA CAGCCAACAT CACTGACTCA GAAGCCTTGG CCAGGTGGCA GCCAGCCATT 5580
GCCACTGTGG ACAGTTATGT CATCTCCTAC ACAGGCGAGA AAGTGCCAGA AATTACACGC 5640
ACGGTGTCCG GGAACACAGT GGAGTATGCT CTGACCGACC TCGAGCCTGC CACGGAATAC 5700
ACACTGAGAA TCTTTGCAGA GAAAGGGCCC CAGAAGAGCT CAACCATCAC TGCCAAGTTC 5760
ACAACAGACC TCGATTCTCC AAGAGACTTG ACTGCTACTG AGGTTCAGTC GGAAACTGCC 5820
CTCCTTACCT GGCGACCCCC CCGGGCATCA GTCACCGGTT ACCTGCTGGT CTATGAATCA 5880
GTGGATGGCA CAGTCAAGGA AGTCATTGTG GGTCCAGATA CCACCTCCTA CAGCCTGGCA 5940
GACCTGAGCC CATCCACCCA CTACACAGCC AAGATCCAGG CACTCAATGG GCCCCTGAGG 6000
AGCAATATGA TCCAGACCAT CTTCACCACA ATTGGACTCC TGTACCCCTT CCCCAAGGAC 6060
TGCTCCCAAG CAATGCTGAA TGGAGACACG ACCTCTGGCC TCTACACCAT TTATCTGAAT 6120
GGTGATAAGG CTCAGGCGCT GGAAGTCTTC TGTGACATGA CCTCTGATGG GGGTGGATGG 6180
ATTGTGTTCC TGAGACGCAA AAACGGACGC GAGAACTTCT ACCAAAACTG GAAGGCATAT 6240
GCTGCTGGAT TTGGGGACCG CAGAGAAGAA TTCTGGCTTG GGCTGGACAA CCTGAACAAA 6300
ATCACAGCCC AGGGGCAGTA CGAGCTCCGG GTGGACCTGC GGGACCATGG GGAGACAGCC 6360
TTTGCTGTCT ATGACAAGTT CAGCGTGGGA GATGCCAAGA CTCGCTACAA GCTGAAGGTG 6420
GAGGGGTACA GTGGGACAGC AGGTGACTCC ATGGCCTACC ACAATGGCAG ATCCTTCTCC 6480
ACCTTTGACA AGGACACAGA TTCAGCCATC ACCAACTGTG CTCTGTCTAC AAGGGGCTTC 6540
TGGTACAGGA ACTGTCACCG TGTCAACCTG ATGGGGAGAT ATGGGGACAA TAACCACAGT 6600
CAGGGCGTTA ACTGGTTCCA CTGGAAGGGC CACGAACACT CAATCCAGTT TGCTGAGATG 6660
AAGCTGAGAC CAAGCAACTT CAGAAATCTT GAAGGCAGGC GCAAACGGGC ATAAATTGGA 6720
GGGACCACTG GGTGAGAGAG GAATAAGGCG GCCCAGAGCG AGGAAAGGAT TTTACCAAAG 6780
CATCAATACA ACCAGCCCAA CCATCGGTCC ACACCTGGGC ATTTGGTGAG AATCAAAGCT 6840
GACCATGGAT CCCTGGGGCC AACGGCAACA GCATGGGCCT CACCTCCTCT GTGATTTCTT 6900
TCTTTGCACC AAAGACATCA GTCTCCAACA TGTTTCTGTT TTGTTGTTTG ATTCAGCAAA 6960
AATCTCCCAG TGACAACATC GCAATAGTTT TTTACTTCTC TTAGGTGGCT CTGGGATGGG 7020
AGAGGGGTAG GATGTACAGG GGTAGTTTGT TTTAGAACCA GCCGTATTTT ACATGAAGCT 7080
GTATAATTAA TTGTCATTAT TTTTGTTAGC AAAGATTAAA TGTGTCATTG GAAGCCATCC 7140
CTTTTTTTAC ATTTCATACA ACAGAAACCA GAAAAGCAAT ACTGTTTCCA TTTTAAGGAT 7200
ATGATTAATA TTATTAATAT AATAATGATG ATGATGATGA TGAAAACTAA GGATTTTTCA 7260
AGAGATCTTT CTTTCCAAAA CATTTCTGGA CAGTACCTGA TTGTATTTTT TTTTTAAATA 7320
AAAGCACAAG TACTTTTGAA AAAAAA 7346

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:

(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

GGTTTGGGTG GAGGTGG 17

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

GGAGGTGGTA CCCCCGG 17

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

GGTGGTACCC CCGG 14

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

GGAGGTGGTA CCCC 14

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

AGAAAGAACG AAAGGAA 17

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GGAGGTGGTA CC 12

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

GGAGCGATGG CTTCCA 16

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

AAAGGAACGG GAGCG 15

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

GGTCGGTTTG GTGG 15

(2) INFORMATION FOR SEQ ID NO: 11

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

CTTACAGGTC CGTTGA 16

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

GGCCGTGTTC GCTGT 15

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

TCACCCCTCT TTCTGG 16

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GGACACCGAC ACGG 14

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

AACGGGAGCG ATGG 14

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

ATCTCGGGGT CGTC 14

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

AAAGAACGAA AGGAA 15

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

GGTGGTACCC C 11

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

CCCGGTACTG A 11

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..13

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

CCACAGAAAG AAC 13

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

GGTTTGGGTG GAGGTGG 17

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

GGAGGTGGTA CCCCCGG 17

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

GGTGGTACCC CCGG 14

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GGAGGTGGTA CCCC 14

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

AGAAAGAACG AAAGGAA 17

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

GGAGGTGGTA CC 12

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

GGAGCGATGG CTTCCA 16

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

AAAGGAACGG GAGCG 15

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

GGTCGGTTTG GGTGG 15

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

CTTACAGGTC CGTTGA 16

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

GGCCGTGTTC GCTGT 15

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

TCACCCCTCT TTCTGG 16

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

GGACACCGAC ACGG 14

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

AACGGGAGCG ATGG 14

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

ATCTCGGGGT CGTC 14

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

AAAGAACGAA AGGAA 15

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

GGTGGTACCC C 11

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

CCCGGTACTG A 11

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..13

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

CCACAGAAAG AAC 13

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

GGTTTGGGTG GAGGTGG 17

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

GGAGGTGGTA CCCCCGG 17

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

GGTGGTACCC CCGG 14

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon

(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

GGAGGTGGTA CCCC 14

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..17

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

AGAAAGAACG AAAGGAA 17

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..12

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

GGAGGTGGTA CC 12

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

GGAGCGATGG CTTCCA 16

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

AAAGGAACGG GAGCG 15

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

GGTCGGTTTG GGTGG 15

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

CTTACAGGTC CGTTGA 16

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

GGCCGTGTTC GCTGT 15

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 16 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..16

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

TCACCCCTCT TTCTGG 16

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

GGACACCGAC ACGG 14

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

AACGGGAGCG ATGG 14

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 14 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..14

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

ATCTCGGGGT CGTC 14

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

AAAGAACGAA AGGAA 15

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

GGTGGTACCC C 11

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..11

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

CCCGGTACTG A 11

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(ix) FEATURE:
(A) NAME/KEY: exon
(B) LOCATION:1..13

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

CCACAGAAAG AAC 13